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NUCLEIC ACID ENCODING HUMAN G PROTEIN-COUPLED RECEPTOR

This patent document is a continuation of U.S. Serial Number 09/875,076, filed June 6, 2001, which is a divisional of U.S. Serial Number 09/417,044, filed October 12, 1999, and claims benefit of priority based upon the following applications, all filed via U.S. Express Mail on the indicated filing dates: U.S. Provisional No. 60/121,852, filed Feb. 26, 1999 claiming the benefit of U.S. Provisional No. 60/109,213, filed Nov. 20, 1998; U.S. Provisional No. 60/120,416, filed Feb. 16, 1999; U.S. Provisional Number 60/123,946, filed Mar. 12, 1999; U.S. Provisional No. 60/123,949, filed Mar. 12, 1999; U.S. Provisional No. 60/136,436, filed May 28, 1999; U.S. Provisional No. 60/136,439, filed May 28, 1999; U.S. Provisional No. 60/136,567, filed May 28, 1999; U.S. Provisional No. 60/137,127, filed May 28, 1999; U.S. Provisional Number 60/137,131, filed May 28, 1999; U.S. Provisional No. 141,448, filed June 29, 1999; U.S. Provisional No. 60/136,437, filed May 28, 1999, U.S. Provisional Number 60/156,653, filed Sep. 29, 1999; U.S. Provisional No. 60/156,333, filed Sep. 29, 1999; U.S. Provisional No. 60/156,555, filed Sep. 29, 1999; U.S. Provisional No. 60/156,634, filed Sep. 29, 1999; U.S. Provisional No. 60/157,280, filed Oct. 1, 1999; U.S. Provisional Number 60/157,294, filed Oct. 1, 1999; U.S. Provisional Number 60/157,281, filed Oct. 1, 1999; U.S. Provisional Number 60/157,293, filed Oct. 1, 1999; U.S. Provisional Number 60/157,282, filed Oct. 1, 1999. Each of the foregoing applications are incorporated herein by reference in their entirety.

U.S. Ser. No. 09/170,496 filed Oct. 13, 1999, now U.S. Patent No. 6,555,339; U.S. Serial Number 09/416,760, filed on Oct. 12, 1999, (now abandoned); and U.S. Ser. No. 09/364,425, filed Jul. 30, 1999, now pending, are each incorporated by reference in its entirety.

All references contained herein, whether to issued patents, patent applications, or non-patent references are hereby incorporated in their entirety for any purpose.

FIELD OF THE INVENTION

The invention disclosed in this patent document relates to transmembrane receptors, and more particularly to endogenous, orphan, human G protein-coupled receptors (“GPCRs”).

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2% or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as “known” receptors, while receptors for which the endogenous ligand has not been identified are referred to as “orphan” receptors. GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, 60% of all prescription pharmaceuticals have been developed. This distinction is not merely semantic, particularly in the case of GPCRs. Thus, the orphan GPCRs are to the pharmaceutical industry what gold was to California in the late 19th century – an opportunity to drive growth, expansion, enhancement and development.

GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, *i.e.*, transmembrane-1 (TM-1), transmebrane-2 (TM-2), etc.). The transmembrane helices

are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or “extracellular” side, of the cell membrane (these are referred to as “extracellular” regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or “intracellular” side, of the cell membrane (these are referred to as “intracellular” regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The “carboxy” (“C”) terminus of the receptor lies in the intracellular space within the cell, and the “amino” (“N”) terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as “activation” of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular “G-protein.” It has been reported that GPCRs are “promiscuous” with respect to G proteins, *i.e.*, that a GPCR can interact with more than one G protein. *See*, Kenakin, T., 43 *Life Sciences* 1095 (1988). Although other G proteins exist, currently, Gq, Gs, Gi, and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein begins a signaling cascade process (referred to as “signal transduction”). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an “inactive” state and an “active” state. A receptor in an inactive state is unable to link to the intracellular signaling

transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response. A receptor may be stabilized in an active state by an endogenous ligand or a compound such as a drug.

SUMMARY OF THE INVENTION

Disclosed herein are human endogenous orphan G protein-coupled receptors.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and **1B** provide reference “grids” for certain dot-blot analyses provided herein (*see also*, Figure 2A and 2B, respectively).

Figures 2A and **2B** provide reproductions of the results of certain dot-blot analyses resulting from hCHN3 and hCHN8, respectively (*see also*, Figures 1A and 1B, respectively).

Figure 3 provides a reproduction of the results of RT-PCR analysis of hRUP3.

Figure 4 provides a reproduction of the results of RT-PCR analysis of hRUP4.

Figure 5 provides a reproduction of the results of RT-PCR analysis of hRUP6.

DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AMINO ACID ABBREVIATIONS used herein are set out in Table 1:

TABLE 1		
ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

COMPOSITION means a material comprising at least one component.

ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention disclosed herein, the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

NON-ORPHAN RECEPTOR shall mean an endogenous naturally occurring molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

VECTOR in reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

A. Identification of Human GPCRs

The efforts of the Human Genome project have led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins. Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of GPCRs, disclosed herein, were discovered by reviewing the GenBank™ database, while other GPCRs were discovered by utilizing a nucleic acid sequence of a GPCR, previously sequenced, to conduct a BLAST™ search of the EST database. **Table A**, below, lists the disclosed endogenous orphan GPCRs along with a GPCR's respective homologous GPCR:

TABLE A

Disclosed Human Orphan GPCRs	Accession Number Identified	Open Reading Frame (Base Pairs)	Per Cent Homology To Designated GPCR	Reference To Homologous GPCR (Accession No.)
hARE-3	AL033379	1,260 bp	52.3% LPA-R	U92642
hARE-4	AC006087	1,119 bp	36% P2Y5	AF000546
hARE-5	AC006255	1,104 bp	32% <i>Oryzias latipes</i>	D43633
hGPR27	AA775870	1,128 bp		
hARE-1	AI090920	999 bp	43% KIAA0001	D13626
hARE-2	AA359504	1,122 bp	53% GPR27	
hPPR1	H67224	1,053 bp	39% EBI1	L31581
hG2A	AA754702	1,113 bp	31% GPR4	L36148
hRUP3	AL035423	1,005 bp	30% <i>Drosophila melanogaster</i>	2133653
hRUP4	AI307658	1,296 bp	32% pNPGPR 28% and 29 % <i>Zebra fish</i> Ya and Yb, respectively	NP_004876 AAC41276 and AAB94616
hRUP5	AC005849	1,413 bp	25% DEZ 23% FMLPR	Q99788 P21462
hRUP6	AC005871	1,245 bp	48% GPR66	NP_006047

hRUP7	AC007922	1,173 bp	43% H3R	AF140538
hCHN3	EST 36581	1,113 bp	53% GPR27	
hCHN4	AA804531	1,077 bp	32% thrombin	4503637
hCHN6	EST 2134670	1,503 bp	36% edg-1	NP_001391
hCHN8	EST 764455	1,029 bp	47% KIAA0001	D13626
hCHN9	EST 1541536	1,077 bp	41% LTB4R	NM_000752
hCHN10	EST 1365839	1,055 bp	35% P2Y	NM_002563

Receptor homology is useful in terms of gaining an appreciation of a role of the disclosed receptors within the human body. Additionally, such homology can provide insight as to possible endogenous ligand(s) that may be natural activators for the disclosed orphan GPCRs.

The ARE-2 receptor disclosed herein was discovered by screening a human genomic library using EST clone 68530 (GenBank Accession Number AA359504). An analysis of this sequence by the named inventor herein has led to the discovery of a 1,122 base-pair open reading-frame, and upon analysis thereof, this open reading-frame sequence evidences sequence homology with the human GPR27, seven-transmembrane receptor.

The nucleic-acid sequence of the novel human receptor ARE-2 is set forth in SEQ.ID.NO.19 and the putative amino acid sequence thereof is set forth in SEQ.ID.NO.20. An alignment report comparing the sequence set forth in SEQ.ID.NO.20 and the reported amino acid sequence for the human GPR27, seven-transmembrane receptor (*see* Figure 1) indicates there is a 53% sequence homology between these receptors.

B. Receptor Screening

Techniques have become more readily available over the past few years for endogenous-ligand identification (this, primarily, for the purpose of providing a means of conducting receptor-binding assays that require a receptor's endogenous ligand)

because the traditional study of receptors has always proceeded from the a priori assumption (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand. This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

As is known in the art, GPCRs can be “active” in their endogenous state even without the binding of the receptor’s endogenous ligand thereto. Such naturally-active receptors can be screened for the direct identification (*i.e.*, without the need for the receptor’s endogenous ligand) of, in particular, inverse agonists. Alternatively, the receptor can be “activated” via, *e.g.*, mutation of the receptor to establish a non-endogenous version of the receptor that is active in the absence of the receptor’s endogenous ligand.

Screening candidate compounds against an endogenous or non-endogenous, constitutively activated version of the human orphan GPCRs disclosed herein can

provide for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. By determining areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed, it is possible to determine related disease/disorder states which are associated with the expression and/or over-expression of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of human orphan GPCRs disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR typically nears the TM6/IC3 interface (such proline residue appears to be quite conserved). By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue, such activation may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

C. Disease/Disorder Identification and/or Selection

Preferably, the DNA sequence of the human orphan GPCR can be used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression of the receptor in tissue samples. The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

D. Screening of Candidate Compounds

1. Generic GPCR screening assay techniques

When a G protein receptor becomes constitutively active (i.e., active in the absence of endogenous ligand binding thereto), it binds to a G protein (*e.g.*, Gq, Gs, Gi, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, [³⁵S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that [³⁵S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the “generic” G protein-coupled receptor assay (*i.e.*, an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the “generic” assay may not bind to the receptor, but may instead merely “uncouple” the G protein from the intracellular domain.

a. Gs and Gi.

Gs stimulates the enzyme adenylyl cyclase. Gi (and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP;

thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple the Gi (or Go) protein are associated with decreased cellular levels of cAMP. *See, generally*, “Indirect Mechanisms of Synaptic Transmission,” Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor (CREB) which then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*, β -galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of the reporter protein. The reporter protein such as β -galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

b. Go and Gq.

Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP₂, releasing two intracellular messengers: diacylglycerol (DAG) and inistol 1,4,5-triphoisphate (IP₃). Increased accumulation of IP₃ is associated with activation of Gq- and Go-associated receptors.

See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992).

Assays that detect IP₃ accumulation can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to a Gq- or Go-associated receptor (*i.e.*, such a compound would decrease the levels of IP₃). Gq-associated receptors can also be examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

3. GPCR Fusion Protein

The use of an endogenous, constitutively activated orphan GPCR, or a non-endogenous, constitutively activated orphan GPCR, for screening of candidate compounds for the direct identification of inverse agonists, agonists and partial agonists provides a unique challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, it is often useful that an approach be utilized that can enhance the signal obtained by the activated receptor. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that a GPCR is or has been constitutively activated, using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR. Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein.

Thus, by definition, in such a system, the constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling with the GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques, although the GPCR Fusion Protein can also be (and preferably is) used with an endogenous, constitutively activated GPCR. This is important in facilitating a significant “signal to noise” ratio; such a significant ratio is import preferred for the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is that the GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the GPCR is upstream of the G protein sequence) and that the “stop” codon of the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12, although this number can be readily ascertained by one of ordinary skill in the art). We have a preference (based upon convenience) of use of a spacer in that some restriction sites that are not used will,

effectively, upon expression, become a spacer. Most preferably, the G protein that couples to the GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

E. Other Utility

Although a preferred use of the human orphan GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists, agonists or partial agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling cascade. The value in human orphan GPCRs is that its utility as a research tool is enhanced in that by determining the location(s) of such receptors within the body, the GPCRs can be used to understand the role of these receptors in the human body before the endogenous ligand therefor is identified. Other uses of the disclosed receptors will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the

ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. Unless otherwise indicated below, all nucleic acid sequences for the disclosed endogenous orphan human GPCRs have been sequenced and verified. For purposes of equivalent receptors, those of ordinary skill in the art will readily appreciate that conservative substitutions can be made to the disclosed sequences to obtain a functionally equivalent receptor.

Example 1

ENDOGENOUS HUMAN GPCRS

1. Identification of Human GPCRs

Several of the disclosed endogenous human GPCRs were identified based upon a review of the GenBank database information. While searching the database, the following cDNA clones were identified as evidenced below.

Disclosed Human Orphan GPCRs	Accession Number	Complete DNA Sequence (Base Pairs)	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID. NO.	Amino Acid SEQ.ID. NO.
hARE-3	AL033379	111,389 bp	1,260 bp	1	2
hARE-4	AC006087	226,925 bp	1,119 bp	3	4
hARE-5	AC006255	127,605 bp	1,104 bp	5	6
hRUP3	AL035423	140,094 bp	1,005 bp	7	8
hRUP5	AC005849	169,144 bp	1,413 bp	9	10
hRUP6	AC005871	218,807 bp	1,245 bp	11	12
hRUP7	AC007922	158,858 bp	1,173 bp	13	14

Other disclosed endogenous human GPCRs were identified by conducting a BLAST search of EST database (dbest) using the following EST clones as query sequences. The following EST clones identified were then used as a probe to screen a human genomic library.

Disclosed Human Orphan GPCRs	Query (Sequence)	EST Clone/ Accession No. Identified	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID.NO.	Amino Acid SEQ.ID.NO.
hGPCR27	Mouse	AA775870	1,125 bp	15	16

	GPCR27				
hARE-1	TDAG	1689643 AI090920	999 bp	17	18
hARE-2	GPCR27	68530 AA359504	1,122 bp	19	20
hPPR1	Bovine PPR1	238667 H67224	1,053 bp	21	22
hG2A	Mouse 1179426	<i>See Example 2(a), below</i>	1,113 bp	23	24
hCHN3	N.A.	EST 36581 (full length)	1,113 bp	25	26
hCHN4	TDAG	1184934 AA804531	1,077 bp	27	28
hCHN6	N.A.	EST 2134670 (full length)	1,503 bp	29	30
hCHN8	KIAA0001	EST 764455	1,029 bp	31	32
hCHN 9	1365839	EST 1541536	1,077 bp	33	34
hCHN10	Mouse EST 1365839	Human 1365839	1,005 bp	35	36
hRUP4	N.A.	AI307658	1,296 bp	37	38

N.A. = "not applicable".

1.a Identification of Human ARE-2

The disclosed human ARE-2 was identified based upon the use of EST database information. The nucleic acid sequence of human GPCR27 was used to conduct a BLAST search of the EST database ("dbest" search). EST clone 68530 (Genbank Accession Number AA359504) was identified from this search and then used as a probe to screen a human genomic library (Stratagene, #942503), following manufacturer instructions. This resulted in a positive genomic clone; the fragment containing a coding sequence was localized with restriction mapping and Southern blot analysis. This fragment was then subcloned into pBluscript (Stratagene), followed by sequencing (SEQ.ID.NO.:1) of human ARE-2. This sequence was then sub-cloned into pCMV (*see infra*). The putative amino acid sequence for ARE-2 is set forth in SEQ.ID.NO.:2.

1.b Preparation of Non-Endogenous, Constitutively Activated ARE-2

Preparation of the non-endogenous human ARE-2 receptor that may evidence constitutive activation of the receptor disclosed herein may be accomplished by

creating a mutation at position 285G, most preferably an G285K mutation. Mutagenesis can preferably be performed using a Transformer Site-Directed™ Mutagenesis Kit (Clontech) according to manufacturer's instructions. The two mutagenesis primers are to be utilized, a lysine mutagenesis oligonucleotide that creates the lysine mutation at amino acid position 285G (*e.g.*, changing GGC to AAA at nucleotides 853-855) and a selection marker oligonucleotide.

2. Full Length Cloning

a. hG2A (Seq. Id. Nos. 23 & 24)

Mouse EST clone 1179426 was used to obtain a human genomic clone containing all but three amino acid hG2A coding sequences. The 5' end of this coding sequence was obtained by using 5'RACE™, and the template for PCR was Clontech's Human Spleen Marathon-ready™ cDNA. The disclosed human G2A was amplified by PCR using the G2A cDNA specific primers for the first and second round PCR as shown in SEQ.ID.NO.: 39 and SEQ.ID.NO.:40 as follows:

5'-CTGTGTACAGCAGTTCGCAGAGTG-3' (SEQ.ID.NO.: 39; 1st round PCR)

5'-GAGTGCCAGGCAGAGCAGGTAGAC-3' (SEQ.ID.NO.: 40; second round PCR).

PCR was performed using Advantage™ GC Polymerase Kit (Clontech; manufacturing instructions will be followed), at 94°C for 30 sec followed by 5 cycles of 94°C for 5 sec and 72°C for 4 min; and 30 cycles of 94° for 5 sec and 70° for 4 min. An approximate 1.3 Kb PCR fragment was purified from agarose gel, digested with Hind III and Xba I and cloned into the expression vector pRC/CMV2 (Invitrogen). The cloned-insert was sequenced using the T7 Sequenase™ kit (USB Amersham; manufacturer instructions will be followed) and the sequence was compared with the presented sequence. Expression of the human G2A will be

detected by probing an RNA dot blot (Clontech; manufacturer instructions will be followed) with the P³²-labeled fragment.

b. hCHN9 (Seq. Id. Nos. 33 & 34)

Sequencing of the EST clone 1541536 indicated that hCHN9 is a partial cDNA clone having only an initiation codon; *i.e.*, the termination codon was missing. When hCHN9 was used to “blast” against the data base (nr), the 3’ sequence of hCHN9 was 100% homologous to the 5’ untranslated region of the leukotriene B4 receptor cDNA, which contained a termination codon in the frame with hCHN9 coding sequence. To determine whether the 5’ untranslated region of LTB4R cDNA was the 3’ sequence of hCHN9, PCR was performed using primers based upon the 5’ sequence flanking the initiation codon found in hCHN9 and the 3’ sequence around the termination codon found in the LTB4R 5’ untranslated region. The 5’ primer sequence utilized was as follows:

5’-CCCGAATTCCTGCTTGCTCCCAGCTTGGCCC-3’ (SEQ.ID.NO.: 41; sense) and

5’-TGTGGATCCTGCTGTCAAAGGTCCCATTCCGG-3’ (SEQ.ID.NO.: 42; antisense).

PCR was performed using thymus cDNA as a template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 65°C for 1min and 72 °C for 1 min and 10 sec. A 1.1kb fragment consistent with the predicted size was obtained from PCR. This PCR fragment was subcloned into pCMV (*see* below) and sequenced (*see*, SEQ.ID.NO.: 33).

c. hRUP 4 (Seq. Id. Nos. 37 & 38)

The full length hRUP4 was cloned by RT-PCR with human brain cDNA (Clontech) as templates:

5’-TCACAATGCTAGGTGTGGTC-3’ (SEQ.ID.NO.: 43; sense) and

5'-TGCATAGACAATGGGATTACAG-3' (SEQ.ID.NO.: 44; antisense).

PCR was performed using TaqPlus™ Precision™ polymerase (Stratagene; manufacturing instructions will be followed) by the following cycles: 94°C for 2 min; 94°C 30 sec; 55°C for 30 sec, 72°C for 45 sec, and 72°C for 10 min. Cycles 2 through 4 were repeated 30 times.

The PCR products were separated on a 1% agarose gel and a 500 bp PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and sequenced using the T7 DNA Sequenase™ kit (Amsham) and the SP6/T7 primers (Stratagene). Sequence analysis revealed that the PCR fragment was indeed an alternatively spliced form of AI307658 having a continuous open reading frame with similarity to other GPCRs. The completed sequence of this PCR fragment was as follows:

5'-TCACAATGCTAGGTGTGGTCTGGCTGGTGGCAGTCATCGTAGGATCACCCATGTGGCAC
GTGCAACAACCTTGAGATCAAATATGACTTCCTATATGAAAAGGAACACATCTGCTGCTTA
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TCCATCTGTAATCCCATTGTCTATGCA-3' (SEQ.ID.NO.: 45)

Based on the above sequence, two sense oligonucleotide primer sets:

5'-CTGCTTAGAAGAGTGGACCAG-3' (SEQ.ID.NO.: 46; oligo 1),

5'-CTGTGCACCAGAAGATCTACAC-3' (SEQ.ID.NO.: 47; oligo 2)

and two antisense oligonucleotide primer sets:

5'-CAAGGATGAAGGTGGTGTAGA-3' (SEQ.ID.NO.: 48; oligo 3)

5'-GTGTAGATCTTCTGGTGCACAGG-3' (SEQ.ID.NO.: 49; oligo 4)

were used for 3'- and 5'-race PCR with a human brain Marathon-Ready™ cDNA (Clontech, Cat# 7400-1) as template, according to manufacture's instructions. DNA fragments generated by the RACE PCR were cloned into the pCRII-TOPO™ vector

(Invitrogen) and sequenced using the SP6/T7 primers (Stratagene) and some internal primers. The 3' RACE product contained a poly(A) tail and a completed open reading frame ending at a TAA stop codon. The 5' RACE product contained an incomplete 5' end; *i.e.*, the ATG initiation codon was not present.

Based on the new 5' sequence, oligo 3 and the following primer:

5'-GCAATGCAGGTCATAGTGAGC-3' (SEQ.ID.NO.: 50; oligo 5)

were used for the second round of 5' RACE PCR and the PCR products were analyzed as above. A third round of 5' RACE PCR was carried out utilizing antisense primers:

5'-TGGAGCATGGTGACGGAATGCAGAAG-3' (SEQ.ID.NO.: 51; oligo 6) and

5'-GTGATGAGCAGGTCACTGAGCGCCAAG-3' (SEQ.ID.NO.: 52; oligo 7).

The sequence of the 5' RACE PCR products revealed the presence of the initiation codon ATG, and further round of 5' RACE PCR did not generate any more 5' sequence. The completed 5' sequence was confirmed by RT-PCR using sense primer 5'-GCAATGCAGGCGCTTAACATTAC-3' (SEQ.ID.NO.: 53; oligo 8) and oligo 4 as primers and sequence analysis of the 650 bp PCR product generated from human brain and heart cDNA templates (Clontech, Cat# 7404-1). The completed 3' sequence was confirmed by RT-PCR using oligo 2 and the following antisense primer:

5'-TTGGGTTACAATCTGAAGGGCA-3' (SEQ.ID.NO.: 54; oligo 9)

and sequence analysis of the 670 bp PCR product generated from human brain and heart cDNA templates. (Clontech, Cat# 7404-1).

d. hRUP5 (Seq. Id. Nos. 9 & 10)

The full length hRUP5 was cloned by RT-PCR using a sense primer upstream from ATG, the initiation codon (SEQ.ID.NO.: 55), and an antisense primer

containing TCA as the stop codon (SEQ.ID.NO.: 56), which had the following sequences:

5'-ACTCCGTGTCCAGCAGGACTCTG-3' (SEQ.ID.NO.:55)

5'-TGCGTGTTCTGACCCTCACGTG-3' (SEQ.ID.NO.: 56)

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following cycle with step 2 through step 4 repeated 30 times: 94°C for 30 sec; 94° for 15 sec; 69° for 40 sec; 72°C for 3 min; and 72°C fro 6 min. A 1.4kb PCR fragment was isolated and cloned with the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the T7 DNA Sequenase™ kit (Amsham). *See*, SEQ.ID.NO.: 9.

e. hRUP6 (Seq. Id. Nos. 11 & 12)

The full length hRUP6 was cloned by RT-PCR using primers:

5'-CAGGCCTTGGATTTTAATGTCAGGGATGG-3' (SEQ.ID.NO.: 57) and

5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 58);

and human thymus Marathon-Ready™ cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech, according to manufacturer's instructions) was used for the amplification in a 50ul reaction by the following cycle: 94°C for 30sec; 94°C for 5 sec; 66°C for 40sec; 72°C for 2.5 sec and 72°C for 7 min. Cycles 2 through 4 were repeated 30 times. A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (*see*, SEQ.ID.NO.: 11) using the ABI Big Dye Terminator™ kit (P.E. Biosystem).

f. hRUP7 (Seq. Id. Nos. 13 & 14)

The full length RUP7 was cloned by RT-PCR using primers:

5'-TGATGTGATGCCAGATACTAATAGCAC-3' (SEQ.ID.NO.: 59; sense) and

5'-CCTGATTCATTTAGGTGAGATTGAGAC-3' (SEQ.ID.NO.: 60; antisense)

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50 ul reaction by the following cycle with step 2 to step 4 repeated 30 times: 94°C for 2 minutes; 94°C for 15 seconds; 60°C for 20 seconds; 72°C for 2 minutes; 72°C for 10 minutes. A 1.25 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator™ kit (P.E. Biosystem). *See*, SEQ.ID.NO.: 13.

g. hARE-5 (Seq. Id. Nos. 5 & 6)

The full length hARE-5 was cloned by PCR using the hARE5 specific primers 5'-CAGCGCAGGGTGAAGCCTGAGAGC-3' SEQ.ID.NO.: 69 (sense, 5' of initiation codon ATG) and 5'-GGCACCTGCTGTGACCTGTGCAGG-3' SEQ.ID.NO.:70 (antisense, 3' of stop codon TGA) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 96°C, 2 minutes; 96°C, 20 seconds; 58°C, 30 seconds; 72°C, 2 minutes; and 72°C, 10 minutes

A 1.1 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ.ID.NO.:5) using the T7 DNA Sequenase™ kit (Amsham).

h. hARE-4 (Seq. Id. Nos.: 3 & 4)

The full length hARE-4 was cloned by PCR using the hARE-4 specific primers 5'-CTGGTGTGCTCCATGGCATCCC-3' SEQ.ID.NO.:67 (sense, 5' of initiation codon ATG) and 5'-GTAAGCCTCCCAGAACGAGAGG-3' SEQ.ID.NO.: 68 (antisense, 3' of stop codon TGA) and human genomic DNA as template. Taq DNA polymerase (Stratagene) and 5% DMSO was used for the amplification by the following cycle

with step 2 to step 3 repeated 35 times: 94°C, 3 minutes; 94°C, 30 seconds; 59°C, 2 minutes; 72°C, 10 minutes

A 1.12 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ.ID.NO.:3) using the T7 DNA Sequenase™ kit (Amsham).

i. hARE-3 (Seq.Id.Nos.: 1 & 2)

The full length hARE-3 was cloned by PCR using the hARE-3 specific primers 5'-gatcaagcttCCATCCTACTGAAACCATGGTC-3' SEQ.ID.NO.:65 (sense, lower case nucleotides represent Hind III overhang, **ATG** as initiation codon) and 5'-gatcagatctCAGTTCCAATATTCACACCACCGTC-3' SEQ.ID.NO.:66 (antisense, lower case nucleotides represent Xba I overhang, **TCA** as stop codon) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94°C, 3 minutes; 94°C, 1 minute; 55°C, 1 minute; 72°C, 2 minutes; 72°C, 10 minutes.

A 1.3 Kb PCR fragment of predicated size was isolated and digested with Hind III and Xba I, cloned into the pRC/CMV2 vector (Invitrogen) at the Hind III and Xba I sites and completely sequenced (SEQ.ID.NO.:1) using the T7 DNA Sequenase™ kit (Amsham).

j. hRUP3 (Seq. Id. Nos.:7 & 8)

The full length hRUP3 was cloned by PCR using the hRUP3 specific primers 5'-GTCCTGCCACTTCGAGACATGG-3' SEQ.ID.NO.:71 (sense, **ATG** as initiation codon) and 5'-GAAACTTCTCTGCCCTTACCGTC-3' SEQ.ID.NO.:72 (antisense, 3' of stop codon TAA) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step

4 repeated 35 times: 94°C, 3 minutes; 94°C, 1 minute; 58°C, 1 minute; 72°C, 2 minutes; 72°C, 10 minutes

A 1.0 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ.ID.NO.: 7) using the T7 DNA sequenase kit (Amsham).

Example 2

RECEPTOR EXPRESSION

Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretory pathways that have evolved for mammalian systems – thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan. The general procedure for expression of the disclosed GPCRs is as follows.

On day one, 1×10^7 293T cells per 150mm plate were plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 20µg DNA (*e.g.*, pCMV vector; pCMV vector with receptor cDNA, etc.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B will be prepared by mixing 120µl lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B are admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture can be referred to as the

“transfection mixture”. Plated 293T cells are washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture will then be added to the cells, followed by incubation for 4hrs at 37°C/5% CO₂. The transfection mixture was then be removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells will then be incubated at 37°C/5% CO₂. After 72hr incubation, cells can then be harvested and utilized for analysis.

Example 3

TISSUE DISTRIBUTION OF THE DISCLOSED HUMAN GPCRS

Several approaches can be used for determination of the tissue distribution of the GPCRs disclosed herein.

1. Dot-Blot Analysis

Using a commercially available human-tissue dot-blot format, endogenous orphan GPCRs were probed for a determination of the areas where such receptors are localized. cDNA fragments from the GPCRs of Example 1 (radiolabelled) were (or can be) used as the probe: radiolabeled probe was (or can be) generated using the complete receptor cDNA (excised from the vector) using a Prime-It II™ Random Primer Labeling Kit (Stratagene, #300385), according to manufacturer's instructions. A human RNA Master Blot™ (Clontech, #7770-1) was hybridized with the endogenous human GPCR radiolabeled probe and washed under stringent conditions according manufacturer's instructions. The blot was exposed to Kodak BioMax™ Autoradiography film overnight at -80°C. Results are summarized for several receptors in Table B and C (*see* Figures 1A and 1B for a grid identifying the various tissues and their locations, respectively). Exemplary dot-blot results are provided in Figure 2A and 2B for results derived using hCHN3 and hCHN8, respectively.

TABLE B

ORPHAN GPCR	Tissue Distribution (highest levels, relative to other tissues in the dot-blot)
hGPCR27	Fetal brain, Putamen, Pituitary gland, Caudate nucleus
hARE-1	Spleen, Peripheral leukocytes, Fetal spleen
hPPR1	Pituitary gland, Heart, salivary gland, Small intestine, Testis
hRUP3	Pancreas
hCHN3	Fetal brain, Putamen, Occipital cortex
hCHN9	Pancreas, Small intestine, Liver
hCHN10	Kidney, Thyroid

TABLE C

ORPHAN GPCR	Tissue Distribution (highest levels, relative to other tissues in the dot-blot)
hARE-3	Cerebellum left, Cerebellum right, Testis, Accumbens
hGPCR3	Corpus collusum, Caudate nucleus, Liver, Heart, Inter-Ventricular Septum
hARE-2	Cerebellum left, Cerebellum right, Substantia
hCHN8	Cerebellum left, Cerebellum right, Kidney, Lung

2. RT-PCR

a. hRUP3

To ascertain the tissue distribution of hRUP3 mRNA, RT-PCR was performed using hRUP3-specific primers and human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) was utilized for the PCR reaction, using the following reaction cycles in a 40ul reaction: 94°C for 2 min; 94°C for 15 sec; 55°C for 30 sec; 72°C for 1 min; 72° C, for 10 min. Primers were as follows:

5'-GACAGGTACCTTGCCATCAAG-3' (SEQ.ID.NO.: 61; sense)

5'-CTGCACAATGCCAGTGATAAGG-3' (SEQ.ID.NO.: 62; antisense).

20ul of the reaction was loaded onto a 1% agarose gel; results are set forth in Figure 3.

As is supported by the data of Figure 3, of the 16 human tissues in the cDNA panel utilized (brain, colon, heart, kidney, lung, ovary, pancreas, placenta, prostate, skeleton, small intestine, spleen, testis, thymus leukocyte, and liver) a single hRUP3

band is evident only from the pancreas. Additional comparative analysis of the protein sequence of hRUP3 with other GPCRs suggest that hRUP3 is related to GPCRs having small molecule endogenous ligand such that it is predicted that the endogenous ligand for hRUP3 is a small molecule.

b. hRUP4

RT-PCR was performed using hRUP4 oligo's 8 and 4 as primers and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) was used for the amplification in a 40ul reaction by the following cycles: 94°C for 30 seconds, 94°C for 10 seconds, 55°C for 30 seconds, 72°C for 2 minutes, and 72°C for 5 minutes with cycles 2 through 4 repeated 30 times.

20 μ l of the reaction were loaded on a 1% agarose gel to analyze the RT-PCR products, and hRUP4 mRNA was found expressed in many human tissues, with the strongest expression in heart and kidney. (*see*, Figure 4). To confirm the authenticity of the PCR fragments, a 300 bp fragment derived from the 5' end of hRUP4 was used as a probe for the Southern Blot analysis. The probe was labeled with ³²P-dCTP using the Prime-It II™ Random Primer Labeling Kit (Stratagene) and purified using the ProbeQuant™ G-50 micro columns (Amersham). Hybridization was done overnight at 42° C following a 12 hr pre-hybridization. The blot was finally washed at 65°C with 0.1 x SSC. The Southern blot did confirm the PCR fragments as hRUP4.

c. hRUP5

RT-PCR was performed using the following hRUP5 specific primers:

5'-CTGACTTCTTGTTCTGGCAGCAGCGG-3' (SEQ.ID.NO.: 63; sense)

5'-AGACCAGCCAGGGCACGCTGAAGAGTG-3' (SEQ.ID.NO.: 64; antisense)

and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) was used for the amplification in a 40ul reaction by the following cycles: 94°C for 30 sec, 94°C for 10 sec, 62°C for 1.5 min, 72°C for 5 min, and with cycles 2 through 3 repeated 30 times. 20 µl of the reaction were loaded on a 1.5% agarose gel to analyze the RT-PCR products, and hRUP5 mRNA was found expressed only in the peripheral blood leukocytes (*data not shown*).

d. hRUP6

RT-PCR was applied to confirm the expression and to determine the tissue distribution of hRUP6. Oligonucleotides used, based on an alignment of AC005871 and GPR66 segments, had the following sequences:

5'-CCAACACCAGCATCCATGGCATCAAG-3' (SEQ.ID.NO.: 73; sense),

5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 74; antisense)

and the human multiple tissue cDNA panels (MTC, Clontech) were used as templates. PCR was performed using TaqPlus Precision™ polymerase (Stratagene; manufacturing instructions will be followed) in a 40ul reaction by the following cycles: 94°C for 30 sec; 94°C 5 sec; 66°C for 40 sec, 72°C for 2.5 min, and 72°C for 7 min. Cycles 2 through 4 were repeated 30 times.

20 ul of the reaction were loaded on a 1.2% agarose gel to analyze the RT-PCR products, and a specific 760bp DNA fragment representing hRUP6 was expressed predominantly in the thymus and with less expression in the heart, kidney, lung, prostate small intestine and testis. (*see*, Figure 5).

References, including but limited to patent applications, that are cited throughout this patent document, unless otherwise indicated, are incorporated herein by reference. Modifications and extension of the disclosed inventions that are within the purview of

the skilled artisan are encompassed within the above disclosure and the claims that follow.

Although a variety of Vectors are available to those in the art, for purposes of utilization for both endogenous and non-endogenous human GPCRs, it is most preferred that the Vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

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<210> 4

<211> 372

<212> PRT

<213> Homo sapiens

<400> 4

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Leu Ala Ala Gly Leu Pro Leu Asn Ala Leu Ala Leu Trp Val Phe Leu
      35                      40                      45

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Arg Ala Leu Arg Val His Ser Val Val Ser Val Tyr Met Cys Asn Leu
 50 55 60

Ala Ala Ser Asp Leu Leu Phe Thr Leu Ser Leu Pro Val Arg Leu Ser
 65 70 75 80

Tyr Tyr Ala Leu His His Trp Pro Phe Pro Asp Leu Leu Cys Gln Thr
 85 90 95

Thr Gly Ala Ile Phe Gln Met Asn Met Tyr Gly Ser Cys Ile Phe Leu
 100 105 110

Met Leu Ile Asn Val Asp Arg Tyr Ala Ala Ile Val His Pro Leu Arg
 115 120 125

Leu Arg His Leu Arg Arg Pro Arg Val Ala Arg Leu Leu Cys Leu Gly
 130 135 140

Val Trp Ala Leu Ile Leu Val Phe Ala Val Pro Ala Ala Arg Val His
 145 150 155 160

Arg Pro Ser Arg Cys Arg Tyr Arg Asp Leu Glu Val Arg Leu Cys Phe
 165 170 175

Glu Ser Phe Ser Asp Glu Leu Trp Lys Gly Arg Leu Leu Pro Leu Val
 180 185 190

Leu Leu Ala Glu Ala Leu Gly Phe Leu Leu Pro Leu Ala Ala Val Val
 195 200 205

Tyr Ser Ser Gly Arg Val Phe Trp Thr Leu Ala Arg Pro Asp Ala Thr
 210 215 220

Gln Ser Gln Arg Arg Arg Lys Thr Val Arg Leu Leu Leu Ala Asn Leu
 225 230 235 240

Val Ile Phe Leu Leu Cys Phe Val Pro Tyr Asn Ser Thr Leu Ala Val
 245 250 255

Tyr Gly Leu Leu Arg Ser Lys Leu Val Ala Ala Ser Val Pro Ala Arg
 260 265 270

Asp Arg Val Arg Gly Val Leu Met Val Met Val Leu Leu Ala Gly Ala
 275 280 285

Asn Cys Val Leu Asp Pro Leu Val Tyr Tyr Phe Ser Ala Glu Gly Phe
 290 295 300

Arg Asn Thr Leu Arg Gly Leu Gly Thr Pro His Arg Ala Arg Thr Ser
 305 310 315 320

Ala Thr Asn Gly Thr Arg Ala Ala Leu Ala Gln Ser Glu Arg Ser Ala
 325 330 335

Val Thr Thr Asp Ala Thr Arg Pro Asp Ala Ala Ser Gln Gly Leu Leu
 340 345 350

Arg Pro Ser Asp Ser His Ser Leu Ser Ser Phe Thr Gln Cys Pro Gln
 355 360 365

Asp Ser Ala Leu
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 <211> 1107
 <212> DNA
 <213> Homo sapiens

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<210> 6
 <211> 368
 <212> PRT
 <213> Homo sapiens

<400> 6

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Gly Leu Ile Leu Ala Ala Val Val Glu Val Gly Ala Leu Leu Gly Asn
20 25 30

Gly Ala Leu Leu Val Val Val Leu Arg Thr Pro Gly Leu Arg Asp Ala
35 40 45

Leu Tyr Leu Ala His Leu Cys Val Val Asp Leu Leu Ala Ala Ala Ser
50 55 60

Ile Met Pro Leu Gly Leu Leu Ala Ala Pro Pro Pro Gly Leu Gly Arg
65 70 75 80

Val Arg Leu Gly Pro Ala Pro Cys Arg Ala Ala Arg Phe Leu Ser Ala
85 90 95

Ala Leu Leu Pro Ala Cys Thr Leu Gly Val Ala Ala Leu Gly Leu Ala
100 105 110

Arg Tyr Arg Leu Ile Val His Pro Leu Arg Pro Gly Ser Arg Pro Pro
115 120 125

Pro Val Leu Val Leu Thr Ala Val Trp Ala Ala Ala Gly Leu Leu Gly
130 135 140

Ala Leu Ser Leu Leu Gly Pro Pro Pro Ala Pro Pro Pro Ala Pro Ala
145 150 155 160

Arg Cys Ser Val Leu Ala Gly Gly Leu Gly Pro Phe Arg Pro Leu Trp
165 170 175

Ala Leu Leu Ala Phe Ala Leu Pro Ala Leu Leu Leu Leu Gly Ala Tyr
180 185 190

Gly Gly Ile Phe Val Val Ala Arg Arg Ala Ala Leu Arg Pro Pro Arg
195 200 205

Pro Ala Arg Gly Ser Arg Leu Arg Ser Asp Ser Leu Asp Ser Arg Leu
210 215 220

Ser Ile Leu Pro Pro Leu Arg Pro Arg Leu Pro Gly Gly Lys Ala Ala
225 230 235 240

Leu Ala Pro Ala Leu Ala Val Gly Gln Phe Ala Ala Cys Trp Leu Pro
245 250 255

Tyr Gly Cys Ala Cys Leu Ala Pro Ala Ala Arg Ala Ala Glu Ala Glu
 260 265 270
 Ala Ala Val Thr Trp Val Ala Tyr Ser Ala Phe Ala Ala His Pro Phe
 275 280 285
 Leu Tyr Gly Leu Leu Gln Arg Pro Val Arg Leu Ala Leu Gly Arg Leu
 290 295 300
 Ser Arg Arg Ala Leu Pro Gly Pro Val Arg Ala Cys Thr Pro Gln Ala
 305 310 315 320
 Trp His Pro Arg Ala Leu Leu Gln Cys Leu Gln Arg Pro Pro Glu Gly
 325 330 335
 Pro Ala Val Gly Pro Ser Glu Ala Pro Glu Gln Thr Pro Glu Leu Ala
 340 345 350
 Gly Gly Arg Ser Pro Ala Tyr Gln Gly Pro Pro Glu Ser Ser Leu Ser
 355 360 365

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 <212> DNA
 <213> Homo sapiens

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1008

<210> 8

<211> 335

<212> PRT

<213> Homo sapiens

<400> 8

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Leu Ile Ile Ala Thr Asn Thr Leu Val Ala Val Ala Val Leu Leu Leu
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Ile His Lys Asn Asp Gly Val Ser Leu Cys Phe Thr Leu Asn Leu Ala
35 40 45

Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp
50 55 60

Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu
65 70 75 80

Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val
85 90 95

Met Leu Ile Thr Phe Asp Arg Tyr Leu Ala Ile Lys Gln Pro Phe Arg
100 105 110

Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly
115 120 125

Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro
130 135 140

Met Phe Gln Gln Thr Ala Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val
145 150 155 160

Phe His Pro His Phe Val Leu Thr Leu Ser Cys Val Gly Phe Phe Pro
165 170 175

Ala Met Leu Leu Phe Val Phe Phe Tyr Cys Asp Met Leu Lys Ile Ala
180 185 190

Ser Met His Ser Gln Gln Ile Arg Lys Met Glu His Ala Gly Ala Met
195 200 205

Ala Gly Gly Tyr Arg Ser Pro Arg Thr Pro Ser Asp Phe Lys Ala Leu
210 215 220

Arg Thr Val Ser Val Leu Ile Gly Ser Phe Ala Leu Ser Trp Thr Pro
225 230 235 240

Phe Leu Ile Thr Gly Ile Val Gln Val Ala Cys Gln Glu Cys His Leu
245 250 255

Tyr Leu Val Leu Glu Arg Tyr Leu Trp Leu Leu Gly Val Gly Asn Ser
260 265 270

Leu Leu Asn Pro Leu Ile Tyr Ala Tyr Trp Gln Lys Glu Val Arg Leu
275 280 285

Gln Leu Tyr His Met Ala Leu Gly Val Lys Lys Val Leu Thr Ser Phe
290 295 300

Leu Leu Phe Leu Ser Ala Arg Asn Cys Gly Pro Glu Arg Pro Arg Glu
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Ser Ser Cys His Ile Val Thr Ile Ser Ser Ser Glu Phe Asp Gly
325 330 335

<210> 9

<211> 1413

<212> DNA

<213> Homo sapiens

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<211> 468

<212> PRT

<213> Homo sapiens

<400> 10

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			20					25					30		
Thr	Val	Phe	Leu	Val	Ala	Leu	Leu	Leu	Leu	Gly	Leu	Pro	Ala	Asn	Gly
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Leu	Met	Ala	Trp	Leu	Ala	Gly	Ser	Gln	Ala	Arg	His	Gly	Ala	Gly	Thr
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Arg	Leu	Ala	Leu	Leu	Leu	Leu	Ser	Leu	Ala	Leu	Ser	Asp	Phe	Leu	Phe
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Leu	Ala	Ala	Ala	Ala	Phe	Gln	Ile	Leu	Glu	Ile	Arg	His	Gly	Gly	His
				85					90					95	
Trp	Pro	Leu	Gly	Thr	Ala	Ala	Cys	Arg	Phe	Tyr	Tyr	Phe	Leu	Trp	Gly
		100						105					110		
Val	Ser	Tyr	Ser	Ser	Gly	Leu	Phe	Leu	Leu	Ala	Ala	Leu	Ser	Leu	Asp
		115					120						125		
Arg	Cys	Leu	Leu	Ala	Leu	Cys	Pro	His	Trp	Tyr	Pro	Gly	His	Arg	Pro
	130					135					140				
Val	Arg	Leu	Pro	Leu	Trp	Val	Cys	Ala	Gly	Val	Trp	Val	Leu	Ala	Thr
	145				150					155					160
Leu	Phe	Ser	Val	Pro	Trp	Leu	Val	Phe	Pro	Glu	Ala	Ala	Val	Trp	Trp
			165						170					175	

Tyr Asp Leu Val Ile Cys Leu Asp Phe Trp Asp Ser Glu Glu Leu Ser
 180 185 190

Leu Arg Met Leu Glu Val Leu Gly Gly Phe Leu Pro Phe Leu Leu Leu
 195 200 205

Leu Val Cys His Val Leu Thr Gln Ala Thr Arg Thr Cys His Arg Gln
 210 215 220

Gln Gln Pro Ala Ala Cys Arg Gly Phe Ala Arg Val Ala Arg Thr Ile
 225 230 235 240

Leu Ser Ala Tyr Val Val Leu Arg Leu Pro Tyr Gln Leu Ala Gln Leu
 245 250 255

Leu Tyr Leu Ala Phe Leu Trp Asp Val Tyr Ser Gly Tyr Leu Leu Trp
 260 265 270

Glu Ala Leu Val Tyr Ser Asp Tyr Leu Ile Leu Leu Asn Ser Cys Leu
 275 280 285

Ser Pro Phe Leu Cys Leu Met Ala Ser Ala Asp Leu Arg Thr Leu Leu
 290 295 300

Arg Ser Val Leu Ser Ser Phe Ala Ala Ala Leu Cys Glu Glu Arg Pro
 305 310 315 320

Gly Ser Phe Thr Pro Thr Glu Pro Gln Thr Gln Leu Asp Ser Glu Gly
 325 330 335

Pro Thr Leu Pro Glu Pro Met Ala Glu Ala Gln Ser Gln Met Asp Pro
 340 345 350

Val Ala Gln Pro Gln Val Asn Pro Thr Leu Gln Pro Arg Ser Asp Pro
 355 360 365

Thr Ala Gln Pro Gln Leu Asn Pro Thr Ala Gln Pro Gln Ser Asp Pro
 370 375 380

Thr Ala Gln Pro Gln Leu Asn Leu Met Ala Gln Pro Gln Ser Asp Ser
 385 390 395 400

Val Ala Gln Pro Gln Ala Asp Thr Asn Val Gln Thr Pro Ala Pro Ala
 405 410 415

Ala Ser Ser Val Pro Ser Pro Cys Asp Glu Ala Ser Pro Thr Pro Ser
 420 425 430

Ser His Pro Thr Pro Gly Ala Leu Glu Asp Pro Ala Thr Pro Pro Ala
 435 440 445

Ser Glu Gly Glu Ser Pro Ser Ser Thr Pro Pro Glu Ala Ala Pro Gly
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Ala Gly Pro Thr
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 <211> 1248
 <212> DNA
 <213> Homo sapiens

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 <211> 415
 <212> PRT
 <213> Homo sapiens

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 Leu Ala Phe Leu Cys Gly Pro Arg Arg Ser His Phe Phe Leu Pro Val
 35 40 45
 Ser Val Val Tyr Val Pro Ile Phe Val Val Gly Val Ile Gly Asn Val
 50 55 60
 Leu Val Cys Leu Val Ile Leu Gln His Gln Ala Met Lys Thr Pro Thr
 65 70 75 80
 Asn Tyr Tyr Leu Phe Ser Leu Ala Val Ser Asp Leu Leu Val Leu Leu
 85 90 95
 Leu Gly Met Pro Leu Glu Val Tyr Glu Met Trp Arg Asn Tyr Pro Phe
 100 105 110
 Leu Phe Gly Pro Val Gly Cys Tyr Phe Lys Thr Ala Leu Phe Glu Thr
 115 120 125
 Val Cys Phe Ala Ser Ile Leu Ser Ile Thr Thr Val Ser Val Glu Arg
 130 135 140
 Tyr Val Ala Ile Leu His Pro Phe Arg Ala Lys Leu Gln Ser Thr Arg
 145 150 155 160
 Arg Arg Ala Leu Arg Ile Leu Gly Ile Val Trp Gly Phe Ser Val Leu
 165 170 175
 Phe Ser Leu Pro Asn Thr Ser Ile His Gly Ile Lys Phe His Tyr Phe
 180 185 190
 Pro Asn Gly Ser Leu Val Pro Gly Ser Ala Thr Cys Thr Val Ile Lys
 195 200 205
 Pro Met Trp Ile Tyr Asn Phe Ile Ile Gln Val Thr Ser Phe Leu Phe
 210 215 220
 Tyr Leu Leu Pro Met Thr Val Ile Ser Val Leu Tyr Tyr Leu Met Ala
 225 230 235 240
 Leu Arg Leu Lys Lys Asp Lys Ser Leu Glu Ala Asp Glu Gly Asn Ala
 245 250 255
 Asn Ile Gln Arg Pro Cys Arg Lys Ser Val Asn Lys Met Leu Phe Val
 260 265 270

Leu Val Leu Val Phe Ala Ile Cys Trp Ala Pro Phe His Ile Asp Arg
 275 280 285
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 305 310 315 320
 Ala Val Asn Pro Ile Ile Tyr Asn Leu Leu Ser Arg Arg Phe Gln Ala
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 Ala Phe Gln Asn Val Ile Ser Ser Phe His Lys Gln Trp His Ser Gln
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 His Asp Pro Gln Leu Pro Pro Ala Gln Arg Asn Ile Phe Leu Thr Glu
 355 360 365
 Cys His Phe Val Glu Leu Thr Glu Asp Ile Gly Pro Gln Phe Pro Cys
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 <212> DNA
 <213> Homo sapiens

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ctgttcacaa ttgtcctttc attttattcc tcagcaacag gtcctaaatc agtttggtat 1020
agaattgcat tttggcttca gtggttcaat tcctttgtca atcctctttt gtatccattg 1080
tgtcacaagc gctttcaaaa ggctttcttg aaaatatttt gtataaaaaa gcaacctcta 1140
ccatcacaac acagtcgggc agtatcttct taa 1173

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<210> 14

<211> 390

<212> PRT

<213> Homo sapiens

<400> 14

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Met Pro Asp Thr Asn Ser Thr Ile Asn Leu Ser Leu Ser Thr Arg Val
  1             5             10             15

```

```

Thr Leu Ala Phe Phe Met Ser Leu Val Ala Phe Ala Ile Met Leu Gly
          20             25             30

```

```

Asn Ala Leu Val Ile Leu Ala Phe Val Val Asp Lys Asn Leu Arg His
          35             40             45

```

```

Arg Ser Ser Tyr Phe Phe Leu Asn Leu Ala Ile Ser Asp Phe Phe Val
          50             55             60

```

```

Gly Val Ile Ser Ile Pro Leu Tyr Ile Pro His Thr Leu Phe Glu Trp
          65             70             75             80

```

```

Asp Phe Gly Lys Glu Ile Cys Val Phe Trp Leu Thr Thr Asp Tyr Leu
          85             90             95

```

```

Leu Cys Thr Ala Ser Val Tyr Asn Ile Val Leu Ile Ser Tyr Asp Arg
          100            105            110

```

```

Tyr Leu Ser Val Ser Asn Ala Val Ser Tyr Arg Thr Gln His Thr Gly
          115            120            125

```

```

Val Leu Lys Ile Val Thr Leu Met Val Ala Val Trp Val Leu Ala Phe
          130            135            140

```

```

Leu Val Asn Gly Pro Met Ile Leu Val Ser Glu Ser Trp Lys Asp Glu
          145            150            155            160

```

```

Gly Ser Glu Cys Glu Pro Gly Phe Phe Ser Glu Trp Tyr Ile Leu Ala
          165            170            175

```

```

Ile Thr Ser Phe Leu Glu Phe Val Ile Pro Val Ile Leu Val Ala Tyr

```



```

atggcgaacg cgagcgaagcc ggggtggcagc ggcggcgccg aggcggccgc cctgggcctc 60
aagctggcca cgctcagcct gctgctgtgc gtgagcctag cgggcaacgt gctgttcgcg 120
ctgctgatcg tgcgggagcg cagcctgcac cgcgccccgt actacctgct gctcgacctg 180
tgectggccg acgggctgcg cgcgctcgcc tgctctcccg ccgtcatgct ggcggcgccg 240
cgtgcgccgg ccgcggcggg ggcgcgcggc ggcgcgctgg gctgcaagct gctcgccctc 300
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gccatgctgg tgtgcgcgcg ctggggcgctg gcgctggccg cggccttccc gccagtgtgt 480
gacggcggtg ggcagcgacga ggacgcgcg tgccgcttg agcagcgccg cgacggcgcc 540
cccggcgcg cgggcttctt gctgctgtgt gccgtggtgg tgggcgccac gcacctcgtc 600
tacctccgcc tgctcttctt catccacgac cgcgcgaaga tgcggcccgc gcgcctggtg 660
cccgcggtca gccacgactg gaccttccac ggcccggggc ccaccggcca ggcggccgcc 720
aactggacgg cgggcttcgg ccgcgggccc acgcgcgcgc cgcttggtgg catccggccc 780
gcagggccgg gccgcggcgc gcgcgcctc ctgctgtgtg aagaattcaa gacggagaag 840
aggctgtgca agatgttcta cgcggtcacg ctgctcttcc tgctcctctg ggggccctac 900
gtcgtggcca gctacctgcg ggtcctggtg cggcccgccg ccgtccccc ggcctacctg 960
acggcctccg tgtggctgac cttcgcgcag gccggcatca accccgtcgt gtgcttctc 1020
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```

<210> 16

<211> 375

<212> PRT

<213> Homo sapiens

<400> 16

```

Met Ala Asn Ala Ser Glu Pro Gly Gly Ser Gly Gly Gly Glu Ala Ala
  1             5             10             15

```

```

Ala Leu Gly Leu Lys Leu Ala Thr Leu Ser Leu Leu Leu Cys Val Ser
      20             25             30

```

```

Leu Ala Gly Asn Val Leu Phe Ala Leu Leu Ile Val Arg Glu Arg Ser
      35             40             45

```

```

Leu His Arg Ala Pro Tyr Tyr Leu Leu Leu Asp Leu Cys Leu Ala Asp
      50             55             60

```

```

Gly Leu Arg Ala Leu Ala Cys Leu Pro Ala Val Met Leu Ala Ala Arg
      65             70             75             80

```

```

Arg Ala Ala Ala Ala Ala Gly Ala Pro Pro Gly Ala Leu Gly Cys Lys
      85             90             95

```

```

Leu Leu Ala Phe Leu Ala Ala Leu Phe Cys Phe His Ala Ala Phe Leu
      100            105            110

```

Leu	Leu	Gly	Val	Gly	Val	Thr	Arg	Tyr	Leu	Ala	Ile	Ala	His	His	Arg	115	120	125
Phe	Tyr	Ala	Glu	Arg	Leu	Ala	Gly	Trp	Pro	Cys	Ala	Ala	Met	Leu	Val	130	135	140
Cys	Ala	Ala	Trp	Ala	Leu	Ala	Leu	Ala	Ala	Ala	Phe	Pro	Pro	Val	Leu	145	150	155
Asp	Gly	Gly	Gly	Asp	Asp	Glu	Asp	Ala	Pro	Cys	Ala	Leu	Glu	Gln	Arg	165	170	175
Pro	Asp	Gly	Ala	Pro	Gly	Ala	Leu	Gly	Phe	Leu	Leu	Leu	Leu	Ala	Val	180	185	190
Val	Val	Gly	Ala	Thr	His	Leu	Val	Tyr	Leu	Arg	Leu	Leu	Phe	Phe	Ile	195	200	205
His	Asp	Arg	Arg	Lys	Met	Arg	Pro	Ala	Arg	Leu	Val	Pro	Ala	Val	Ser	210	215	220
His	Asp	Trp	Thr	Phe	His	Gly	Pro	Gly	Ala	Thr	Gly	Gln	Ala	Ala	Ala	225	230	235
Asn	Trp	Thr	Ala	Gly	Phe	Gly	Arg	Gly	Pro	Thr	Pro	Pro	Ala	Leu	Val	245	250	255
Gly	Ile	Arg	Pro	Ala	Gly	Pro	Gly	Arg	Gly	Ala	Arg	Arg	Leu	Leu	Val	260	265	270
Leu	Glu	Glu	Phe	Lys	Thr	Glu	Lys	Arg	Leu	Cys	Lys	Met	Phe	Tyr	Ala	275	280	285
Val	Thr	Leu	Leu	Phe	Leu	Leu	Leu	Trp	Gly	Pro	Tyr	Val	Val	Ala	Ser	290	295	300
Tyr	Leu	Arg	Val	Leu	Val	Arg	Pro	Gly	Ala	Val	Pro	Gln	Ala	Tyr	Leu	305	310	315
Thr	Ala	Ser	Val	Trp	Leu	Thr	Phe	Ala	Gln	Ala	Gly	Ile	Asn	Pro	Val	325	330	335
Val	Cys	Phe	Leu	Phe	Asn	Arg	Glu	Leu	Arg	Asp	Cys	Phe	Arg	Ala	Gln	340	345	350
Phe	Pro	Cys	Cys	Gln	Ser	Pro	Arg	Thr	Thr	Gln	Ala	Thr	His	Pro	Cys	355	360	365

Asp Leu Lys Gly Ile Gly Leu
 370 375

<210> 17
 <211> 1002
 <212> DNA
 <213> Homo sapiens

<400> 17
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 aatactttgg ctctgtgggt gtttggtcac atccccagct cctccacctt catcatctac 180
 ctcaaaaaca ctttgggtggc cgacttgata atgacactca tgcttccttt caaaatcctc 240
 tctgactcac acctggcacc ctggcagctc agagcttttg tgtgtcgttt ttcttcggtg 300
 atattttatg agaccatgta tgtgggcatc gtgctgttag ggctcatagc ctttgacaga 360
 ttcttcaaga tcatcagacc tttgagaaat atttttctaa aaaaacctgt ttttgcaaaa 420
 acggtctcaa tcttcatctg gttctttttg ttcttcatct ccctgccaaa tacgatcttg 480
 agcaacaagg aagcaacacc atcgtctgtg aaaaagtgtg ctctcttaaa ggggcctctg 540
 gggctgaaat ggcatacaat ggtaaataac atatgccagt ttattttctg gactgttttt 600
 atcctaatgc ttgtgtttta tgtggttatt gcaaaaaaag tatatgattc ttatagaaag 660
 tccaaaagta aggacagaaa aaacaacaaa aagctggaag gcaaagtatt tgttgcgtg 720
 gctgtcttct ttgtgtgttt tgctccattt cattttgcca gagttccata tactcacagt 780
 caaaccaaca ataagactga ctgtagactg caaaatcaac tgttttattgc taaagaaaca 840
 actctctttt tggcagcaac taacatttgt atggatccct taatatacat attcttatgt 900
 aaaaaattca cagaaaagct accatgtatg caaggagaa agaccacagc atcaagccaa 960
 gaaaatcata gcagtcagac agacaacata accttaggct ga 1002

<210> 18
 <211> 333
 <212> PRT
 <213> Homo sapiens

<400> 18
 Met Asn Thr Thr Val Met Gln Gly Phe Asn Arg Ser Glu Arg Cys Pro
 1 5 10 15
 Arg Asp Thr Arg Ile Val Gln Leu Val Phe Pro Ala Leu Tyr Thr Val
 20 25 30
 Val Phe Leu Thr Gly Ile Leu Leu Asn Thr Leu Ala Leu Trp Val Phe
 35 40 45
 Val His Ile Pro Ser Ser Ser Thr Phe Ile Ile Tyr Leu Lys Asn Thr
 50 55 60
 Leu Val Ala Asp Leu Ile Met Thr Leu Met Leu Pro Phe Lys Ile Leu

65		70		75		80									
Ser	Asp	Ser	His	Leu	Ala	Pro	Trp	Gln	Leu	Arg	Ala	Phe	Val	Cys	Arg
			85						90					95	
Phe	Ser	Ser	Val	Ile	Phe	Tyr	Glu	Thr	Met	Tyr	Val	Gly	Ile	Val	Leu
			100					105					110		
Leu	Gly	Leu	Ile	Ala	Phe	Asp	Arg	Phe	Leu	Lys	Ile	Ile	Arg	Pro	Leu
		115					120					125			
Arg	Asn	Ile	Phe	Leu	Lys	Lys	Pro	Val	Phe	Ala	Lys	Thr	Val	Ser	Ile
	130					135					140				
Phe	Ile	Trp	Phe	Phe	Leu	Phe	Phe	Ile	Ser	Leu	Pro	Asn	Thr	Ile	Leu
145					150					155					160
Ser	Asn	Lys	Glu	Ala	Thr	Pro	Ser	Ser	Val	Lys	Lys	Cys	Ala	Ser	Leu
			165						170					175	
Lys	Gly	Pro	Leu	Gly	Leu	Lys	Trp	His	Gln	Met	Val	Asn	Asn	Ile	Cys
			180					185					190		
Gln	Phe	Ile	Phe	Trp	Thr	Val	Phe	Ile	Leu	Met	Leu	Val	Phe	Tyr	Val
		195					200					205			
Val	Ile	Ala	Lys	Lys	Val	Tyr	Asp	Ser	Tyr	Arg	Lys	Ser	Lys	Ser	Lys
	210					215					220				
Asp	Arg	Lys	Asn	Asn	Lys	Lys	Leu	Glu	Gly	Lys	Val	Phe	Val	Val	Val
225					230					235					240
Ala	Val	Phe	Phe	Val	Cys	Phe	Ala	Pro	Phe	His	Phe	Ala	Arg	Val	Pro
				245					250					255	
Tyr	Thr	His	Ser	Gln	Thr	Asn	Asn	Lys	Thr	Asp	Cys	Arg	Leu	Gln	Asn
			260					265					270		
Gln	Leu	Phe	Ile	Ala	Lys	Glu	Thr	Thr	Leu	Phe	Leu	Ala	Ala	Thr	Asn
		275					280					285			
Ile	Cys	Met	Asp	Pro	Leu	Ile	Tyr	Ile	Phe	Leu	Cys	Lys	Lys	Phe	Thr
	290					295					300				
Glu	Lys	Leu	Pro	Cys	Met	Gln	Gly	Arg	Lys	Thr	Thr	Ala	Ser	Ser	Gln
305				310						315					320
Glu	Asn	His	Ser	Ser	Gln	Thr	Asp	Asn	Ile	Thr	Leu	Gly			

<210> 19
 <211> 1122
 <212> DNA
 <213> Homo sapiens

<400> 19
 atggccaaca ctaccggaga gcctgaggag gtgagcggcg ctctgtcccc accgtccgca 60
 tcagcttatg tgaagctggt actgctggga ctgattatgt gcgtgagcct ggcgggtaac 120
 gccatcttgt ccctgctggt gctcaaggag cgtgccctgc acaaggctcc ttactacttc 180
 ctgctggacc tgtgcctggc cgatggcata cgctctgccg tctgcttccc ctttgtgctg 240
 gcttctgtgc gccacggctc ttcattggacc ttcagtgcac tcagctgcaa gattgtggcc 300
 tttatggcgc tgctcttttg cttccatgcg gccttcatgc tgttctgcat cagcgtcacc 360
 cgctacatgg ccatcgccca ccaccgcttc tacgccaagc gcatgacact ctggacatgc 420
 gcggctgtca tctgcatggc ctggaccctg tctgtggcca tggccttccc acctgtcttt 480
 gacgtgggca cctacaagtt tattcgggag gaggaccagt gcatctttga gcatcgctac 540
 ttcaaggcca atgacacgct gggcttcatg cttatgttgg ctgtgctcat ggcagctacc 600
 catgctgtct acggcaagct gctcctcttc gagtatcgtc accgcaagat gaagccagtg 660
 cagatggtgc cagccatcag ccagaactgg acattccatg gtcccggggc caccggccag 720
 gctgctgcca actggatcgc cggctttggc cgtgggcccc tgccaccaac cctgctgggt 780
 atccggcaga atgggcatgc agccagccgg cggctactgg gcatggacga ggtcaagggt 840
 gaaaagcagc tgggcccgcg gttctacgcg atcacactgc tctttctgct cctctgggtca 900
 ccctacatcg tggcctgcta ctggcgagtg tttgtgaaag cctgtgctgt gccccaccgc 960
 tacctggcca ctgctgtttg gatgagcttc gcccaggctg ccgtcaaccc aattgtctgc 1020
 ttctgtctca acaaggacct caagaagtgc ctgaccactc acgccccctg ctgggggcaca 1080
 ggaggtgccc cggctcccag agaaccctac tgtgtcatgt ga 1122

<210> 20
 <211> 373
 <212> PRT
 <213> Homo sapiens

<400> 20
 Met Ala Asn Thr Thr Gly Glu Pro Glu Glu Val Ser Gly Ala Leu Ser
 1 5 10 15
 Pro Pro Ser Ala Ser Ala Tyr Val Lys Leu Val Leu Leu Gly Leu Ile
 20 25 30
 Met Cys Val Ser Leu Ala Gly Asn Ala Ile Leu Ser Leu Leu Val Leu
 35 40 45
 Lys Glu Arg Ala Leu His Lys Ala Pro Tyr Tyr Phe Leu Leu Asp Leu
 50 55 60

Cys	Leu	Ala	Asp	Gly	Ile	Arg	Ser	Ala	Val	Cys	Phe	Pro	Phe	Val	Leu	
65					70					75					80	
Ala	Ser	Val	Arg	His	Gly	Ser	Ser	Trp	Thr	Phe	Ser	Ala	Leu	Ser	Cys	
				85					90					95		
Lys	Ile	Val	Ala	Phe	Met	Ala	Val	Leu	Phe	Cys	Phe	His	Ala	Ala	Phe	
			100					105					110			
Met	Leu	Phe	Cys	Ile	Ser	Val	Thr	Arg	Tyr	Met	Ala	Ile	Ala	His	His	
		115					120					125				
Arg	Phe	Tyr	Ala	Lys	Arg	Met	Thr	Leu	Trp	Thr	Cys	Ala	Ala	Val	Ile	
	130					135					140					
Cys	Met	Ala	Trp	Thr	Leu	Ser	Val	Ala	Met	Ala	Phe	Pro	Pro	Val	Phe	
145					150					155					160	
Asp	Val	Gly	Thr	Tyr	Lys	Phe	Ile	Arg	Glu	Glu	Asp	Gln	Cys	Ile	Phe	
			165						170					175		
Glu	His	Arg	Tyr	Phe	Lys	Ala	Asn	Asp	Thr	Leu	Gly	Phe	Met	Leu	Met	
		180						185					190			
Leu	Ala	Val	Leu	Met	Ala	Ala	Thr	His	Ala	Val	Tyr	Gly	Lys	Leu	Leu	
		195					200					205				
Leu	Phe	Glu	Tyr	Arg	His	Arg	Lys	Met	Lys	Pro	Val	Gln	Met	Val	Pro	
	210					215					220					
Ala	Ile	Ser	Gln	Asn	Trp	Thr	Phe	His	Gly	Pro	Gly	Ala	Thr	Gly	Gln	
225				230						235					240	
Ala	Ala	Ala	Asn	Trp	Ile	Ala	Gly	Phe	Gly	Arg	Gly	Pro	Met	Pro	Pro	
			245						250					255		
Thr	Leu	Leu	Gly	Ile	Arg	Gln	Asn	Gly	His	Ala	Ala	Ser	Arg	Arg	Leu	
		260						265					270			
Leu	Gly	Met	Asp	Glu	Val	Lys	Gly	Glu	Lys	Gln	Leu	Gly	Arg	Met	Phe	
		275					280					285				
Tyr	Ala	Ile	Thr	Leu	Leu	Phe	Leu	Leu	Leu	Trp	Ser	Pro	Tyr	Ile	Val	
	290					295					300					
Ala	Cys	Tyr	Trp	Arg	Val	Phe	Val	Lys	Ala	Cys	Ala	Val	Pro	His	Arg	
305					310					315					320	

Glu Met Asn Gly Thr Tyr Asp Tyr Ser Gln Tyr Glu Leu Ile Cys Ile
 20 25 30

Lys Glu Asp Val Arg Glu Phe Ala Lys Val Phe Leu Pro Val Phe Leu
 35 40 45

Thr Ile Ala Phe Val Ile Gly Leu Ala Gly Asn Ser Met Val Val Ala
 50 55 60

Ile Tyr Ala Tyr Tyr Lys Lys Gln Arg Thr Lys Thr Asp Val Tyr Ile
 65 70 75 80

Leu Asn Leu Ala Val Ala Asp Leu Leu Leu Leu Phe Thr Leu Pro Phe
 85 90 95

Trp Ala Val Asn Ala Val His Gly Trp Val Leu Gly Lys Ile Met Cys
 100 105 110

Lys Ile Thr Ser Ala Leu Tyr Thr Leu Asn Phe Val Ser Gly Met Gln
 115 120 125

Phe Leu Ala Cys Ile Ser Ile Asp Arg Tyr Val Ala Val Thr Asn Val
 130 135 140

Pro Ser Gln Ser Gly Val Gly Lys Pro Cys Trp Ile Ile Cys Phe Cys
 145 150 155 160

Val Trp Met Ala Ala Ile Leu Leu Ser Ile Pro Gln Leu Val Phe Tyr
 165 170 175

Thr Val Asn Asp Asn Ala Arg Cys Ile Pro Ile Phe Pro Arg Tyr Leu
 180 185 190

Gly Thr Ser Met Lys Ala Leu Ile Gln Met Leu Glu Ile Cys Ile Gly
 195 200 205

Phe Val Val Pro Phe Leu Ile Met Gly Val Cys Tyr Phe Ile Thr Ala
 210 215 220

Arg Thr Leu Met Lys Met Pro Asn Ile Lys Ile Ser Arg Pro Leu Lys
 225 230 235 240

Val Leu Leu Thr Val Val Ile Val Phe Ile Val Thr Gln Leu Pro Tyr
 245 250 255

Asn Ile Val Lys Phe Cys Arg Ala Ile Asp Ile Ile Tyr Ser Leu Ile
 260 265 270

Thr Ser Cys Asn Met Ser Lys Arg Met Asp Ile Ala Ile Gln Val Thr
 275 280 285
 Glu Ser Ile Ala Leu Phe His Ser Cys Leu Asn Pro Ile Leu Tyr Val
 290 295 300
 Phe Met Gly Ala Ser Phe Lys Asn Tyr Val Met Lys Val Ala Lys Lys
 305 310 315 320
 Tyr Gly Ser Trp Arg Arg Gln Arg Gln Ser Val Glu Glu Phe Pro Phe
 325 330 335
 Asp Ser Glu Gly Pro Thr Glu Pro Thr Ser Thr Phe Ser Ile
 340 345 350

<210> 23
 <211> 1116
 <212> DNA
 <213> Homo sapiens

<400> 23
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 gccaaagacct gcaacaacgt gtccttcgaa gagagcagga tagtcctggt cgtggtgtac 120
 agcgcggtgt gcacgctggg ggtgccggcc aactgcctga ctgcgtggct ggcgctgctg 180
 caggtactgc agggcaacgt gctggccgtc tacctgctct gcctggcact ctgcgaactg 240
 ctgtacacag gcacgctgcc actctgggtc atctatatcc gcaaccagca ccgctggacc 300
 ctaggcctgc tggcctcgaa ggtgaccgcc tacatcttct tctgcaacat ctacgtcagc 360
 atcctcttcc tgtgctgcat ctctgcgac cgcttcgtgg ccgtggtgta cgcgctggag 420
 agtcggggcc gccgccgccg gaggaccgcc atcctcatct ccgcctgcat cttcatcctc 480
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 ctgcagatgg acagcaggat tgccgggtac tactacgcca gggtcacctg tggctttgcc 600
 atccctctct ccatcatcgc cttcaccaac caccggattt tcaggagcat caagcagagc 660
 atgggcttaa gcgctgcca gaaggccaag gtgaagcact cggccatcgc ggtggttgtc 720
 atcttcctag tctgcttcgc cccgtaccac ctggttctcc tcgtcaaagc cgctgccttt 780
 tcctactaca gaggagacag gaacgccatg tgccgcttgg aggaaaggct gtacacagcc 840
 tctgtggtgt ttctgtgctt gtccacggtg aacggcgtgg ctgaccccat tatctacgtg 900
 ctggccacgg accattccc ccaagaagtg tccagaatcc ataaggggtg gaaagagtgg 960
 tccatgaaga cagacgtcac caggctcacc cacagcaggg acaccgagga gctgcagtcg 1020
 cccgtggccc ttgcagacca ctacacctt tccaggcccg tgcacccacc agggtcacca 1080
 tgccctgcaa agaggctgat tgaggagtcc tgctga 1116

<210> 24
 <211> 371
 <212> PRT
 <213> Homo sapiens

<400> 24

Met	Pro	Gly	Asn	Ala	Thr	Pro	Val	Thr	Thr	Thr	Ala	Pro	Trp	Ala	Ser	
1				5					10					15		
Leu	Gly	Leu	Ser	Ala	Lys	Thr	Cys	Asn	Asn	Val	Ser	Phe	Glu	Glu	Ser	
			20					25					30			
Arg	Ile	Val	Leu	Val	Val	Val	Tyr	Ser	Ala	Val	Cys	Thr	Leu	Gly	Val	
		35					40					45				
Pro	Ala	Asn	Cys	Leu	Thr	Ala	Trp	Leu	Ala	Leu	Leu	Gln	Val	Leu	Gln	
		50				55					60					
Gly	Asn	Val	Leu	Ala	Val	Tyr	Leu	Leu	Cys	Leu	Ala	Leu	Cys	Glu	Leu	
65					70					75					80	
Leu	Tyr	Thr	Gly	Thr	Leu	Pro	Leu	Trp	Val	Ile	Tyr	Ile	Arg	Asn	Gln	
				85					90					95		
His	Arg	Trp	Thr	Leu	Gly	Leu	Leu	Ala	Ser	Lys	Val	Thr	Ala	Tyr	Ile	
			100					105					110			
Phe	Phe	Cys	Asn	Ile	Tyr	Val	Ser	Ile	Leu	Phe	Leu	Cys	Cys	Ile	Ser	
		115					120					125				
Cys	Asp	Arg	Phe	Val	Ala	Val	Val	Tyr	Ala	Leu	Glu	Ser	Arg	Gly	Arg	
		130				135					140					
Arg	Arg	Arg	Arg	Thr	Ala	Ile	Leu	Ile	Ser	Ala	Cys	Ile	Phe	Ile	Leu	
145					150					155					160	
Val	Gly	Ile	Val	His	Tyr	Pro	Val	Phe	Gln	Thr	Glu	Asp	Lys	Glu	Thr	
				165					170					175		
Cys	Phe	Asp	Met	Leu	Gln	Met	Asp	Ser	Arg	Ile	Ala	Gly	Tyr	Tyr	Tyr	
			180					185					190			
Ala	Arg	Phe	Thr	Val	Gly	Phe	Ala	Ile	Pro	Leu	Ser	Ile	Ile	Ala	Phe	
		195					200					205				
Thr	Asn	His	Arg	Ile	Phe	Arg	Ser	Ile	Lys	Gln	Ser	Met	Gly	Leu	Ser	
		210				215					220					
Ala	Ala	Gln	Lys	Ala	Lys	Val	Lys	His	Ser	Ala	Ile	Ala	Val	Val	Val	
225					230					235					240	
Ile	Phe	Leu	Val	Cys	Phe	Ala	Pro	Tyr	His	Leu	Val	Leu	Leu	Val	Lys	
				245					250					255		

Ala Ala Ala Phe Ser Tyr Tyr Arg Gly Asp Arg Asn Ala Met Cys Gly
 260 265 270
 Leu Glu Glu Arg Leu Tyr Thr Ala Ser Val Val Phe Leu Cys Leu Ser
 275 280 285
 Thr Val Asn Gly Val Ala Asp Pro Ile Ile Tyr Val Leu Ala Thr Asp
 290 295 300
 His Ser Arg Gln Glu Val Ser Arg Ile His Lys Gly Trp Lys Glu Trp
 305 310 315 320
 Ser Met Lys Thr Asp Val Thr Arg Leu Thr His Ser Arg Asp Thr Glu
 325 330 335
 Glu Leu Gln Ser Pro Val Ala Leu Ala Asp His Tyr Thr Phe Ser Arg
 340 345 350
 Pro Val His Pro Pro Gly Ser Pro Cys Pro Ala Lys Arg Leu Ile Glu
 355 360 365
 Glu Ser Cys
 370

<210> 25
 <211> 1113
 <212> DNA
 <213> Homo sapiens

<400> 25
 atggcgaact atagccatgc agctgacaac attttgcaaa atctctcgcc tctaacagcc 60
 tttctgaaac tgacttcctt gggtttcata ataggagtca gcgtggtggg caacctcctg 120
 atctccattt tgctagtga agataagacc ttgcatagag caccttacta cttcctgttg 180
 gatctttgct gttcagatat cctcagatct gcaatttggt tcccatttgt gttcaactct 240
 gtcaaaaatg gctctacctg gacttatggg actctgactt gcaaagtgat tgcctttctg 300
 ggggttttgt cctgtttcca cactgcttct atgctcttct gcatcagtgt caccagatac 360
 ttagctatcg cccatcaccg cttctataca aagaggctga ccttttggac gtgtctggct 420
 gtgatctgta tgggtgtggac tctgtctgtg gccatggcat ttcccccggt tttagacgtg 480
 ggcacttact cattcattag ggaggaagat caatgcacct tccaacaccg ctccttcagg 540
 gctaattgatt ccttaggatt tatgtctgct cttgctctca tcctcctagc cacacagctt 600
 gtctacctca agctgatatt tttcgtccac gatcgaagaa aaatgaagcc agtccagttt 660
 gtagcagcag tcagccagaa ctggactttt catggtcctg gagccagtgg ccaggcagct 720
 gccaattggc tagcaggatt tggaaggggt cccacaccac ccaccttgct gggcatcagg 780
 caaaatgcaa acaccacagg cagaagaagg ctattggtct tagacgagtt caaaatggag 840
 aaaagaatca gcagaatgtt ctatataatg acttttctgt ttctaacctt gtggggcccc 900
 tacctggtgg cctgttattg gagagttttt gcaagagggc ctgtagtacc aggggggatt 960

ctaacagctg ctgtctggat gagttttgcc caagcaggaa tcaatccttt tgtctgcatt 1020
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 aggttaccaa gggaacctta ctgtgttata tga 1113

<210> 26
 <211> 370
 <212> PRT
 <213> Homo sapiens

<400> 26
 Met Ala Asn Tyr Ser His Ala Ala Asp Asn Ile Leu Gln Asn Leu Ser
 1 5 10 15
 Pro Leu Thr Ala Phe Leu Lys Leu Thr Ser Leu Gly Phe Ile Ile Gly
 20 25 30
 Val Ser Val Val Gly Asn Leu Leu Ile Ser Ile Leu Leu Val Lys Asp
 35 40 45
 Lys Thr Leu His Arg Ala Pro Tyr Tyr Phe Leu Leu Asp Leu Cys Cys
 50 55 60
 Ser Asp Ile Leu Arg Ser Ala Ile Cys Phe Pro Phe Val Phe Asn Ser
 65 70 75 80
 Val Lys Asn Gly Ser Thr Trp Thr Tyr Gly Thr Leu Thr Cys Lys Val
 85 90 95
 Ile Ala Phe Leu Gly Val Leu Ser Cys Phe His Thr Ala Phe Met Leu
 100 105 110
 Phe Cys Ile Ser Val Thr Arg Tyr Leu Ala Ile Ala His His Arg Phe
 115 120 125
 Tyr Thr Lys Arg Leu Thr Phe Trp Thr Cys Leu Ala Val Ile Cys Met
 130 135 140
 Val Trp Thr Leu Ser Val Ala Met Ala Phe Pro Pro Val Leu Asp Val
 145 150 155 160
 Gly Thr Tyr Ser Phe Ile Arg Glu Glu Asp Gln Cys Thr Phe Gln His
 165 170 175
 Arg Ser Phe Arg Ala Asn Asp Ser Leu Gly Phe Met Leu Leu Leu Ala
 180 185 190
 Leu Ile Leu Leu Ala Thr Gln Leu Val Tyr Leu Lys Leu Ile Phe Phe

195	200	205
Val His Asp Arg Arg Lys Met Lys Pro Val Gln Phe Val Ala Ala Val		
210	215	220
Ser Gln Asn Trp Thr Phe His Gly Pro Gly Ala Ser Gly Gln Ala Ala		
225	230	235 240
Ala Asn Trp Leu Ala Gly Phe Gly Arg Gly Pro Thr Pro Pro Thr Leu		
245	250	255
Leu Gly Ile Arg Gln Asn Ala Asn Thr Thr Gly Arg Arg Arg Leu Leu		
260	265	270
Val Leu Asp Glu Phe Lys Met Glu Lys Arg Ile Ser Arg Met Phe Tyr		
275	280	285
Ile Met Thr Phe Leu Phe Leu Thr Leu Trp Gly Pro Tyr Leu Val Ala		
290	295	300
Cys Tyr Trp Arg Val Phe Ala Arg Gly Pro Val Val Pro Gly Gly Phe		
305	310	315 320
Leu Thr Ala Ala Val Trp Met Ser Phe Ala Gln Ala Gly Ile Asn Pro		
325	330	335
Phe Val Cys Ile Phe Ser Asn Arg Glu Leu Arg Arg Cys Phe Ser Thr		
340	345	350
Thr Leu Leu Tyr Cys Arg Lys Ser Arg Leu Pro Arg Glu Pro Tyr Cys		
355	360	365
Val Ile		
370		

<210> 27
 <211> 1080
 <212> DNA
 <213> Homo sapiens

<400> 27
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 gcgatcgagg tggccctgcc cgtggtgtac tcgctggtgg cggcggtcag catcccgggc 120
 aacctcttct ctctgtgggt gctgtgccgg cgcattggggc ccagatcccc gtcggtcatc 180
 ttcattgatca acctgagcgt cacggacctg atgctggcca gcgtgttgcc tttccaaatc 240
 tactaccatt gcaaccgcca ccactgggta ttcgggggtgc tgctttgcaa cgtggtgacc 300
 gtggcctttt acgcaaacat gtattccagc atcctcacca tgacctgtat cagcgtggag 360

cgcttcctgg gggtcctgta cccgctcagc tccaagcgct ggcgccgccg tcgttacgcg 420
 gtggccgcgt gtgcagggac ctggctgctg ctccctgaccg ccctgtgccc gctggcgcg 480
 accgatctca cctaccgggt gcacgccctg ggcacatcatca cctgcttcga cgtcctcaag 540
 tggacgatgc tccccagcgt ggccatgtgg gccgtgttcc tcttcaccat cttcatcctg 600
 ctgttcctca tcccgcttcgt gatcaccgtg gcttggttaca cggccacat cctcaagctg 660
 ttgcgcacgg aggaggcgca cggccgggag cagcggaggc gcgcgggtggg cctggccgcg 720
 gtggtcttgc tggcctttgt cacctgcttc gcccccaaca acttcgtgct cctggcgcac 780
 atcgtgagcc gcctgttcta cggcaagagc tactaccacg tgtacaagct cacgctgtgt 840
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 cagctgcgcc tgcgggaata tttgggctgc cgccgggtgc ccagagacac cctggacacg 960
 cgccgcgaga gcctcttctc cgccaggacc acgtccgtgc gctccgaggc cgggtgcgcac 1020
 cctgaaggga tggagggagc caccaggccc ggcctccaga ggcaggagag tgtgttctga 1080

<210> 28

<211> 359

<212> PRT

<213> Homo sapiens

<400> 28

Met Gln Val Pro Asn Ser Thr Gly Pro Asp Asn Ala Thr Leu Gln Met
 1 5 10 15

Leu Arg Asn Pro Ala Ile Ala Val Ala Leu Pro Val Val Tyr Ser Leu
 20 25 30

Val Ala Ala Val Ser Ile Pro Gly Asn Leu Phe Ser Leu Trp Val Leu
 35 40 45

Cys Arg Arg Met Gly Pro Arg Ser Pro Ser Val Ile Phe Met Ile Asn
 50 55 60

Leu Ser Val Thr Asp Leu Met Leu Ala Ser Val Leu Pro Phe Gln Ile
 65 70 75 80

Tyr Tyr His Cys Asn Arg His His Trp Val Phe Gly Val Leu Leu Cys
 85 90 95

Asn Val Val Thr Val Ala Phe Tyr Ala Asn Met Tyr Ser Ser Ile Leu
 100 105 110

Thr Met Thr Cys Ile Ser Val Glu Arg Phe Leu Gly Val Leu Tyr Pro
 115 120 125

Leu Ser Ser Lys Arg Trp Arg Arg Arg Arg Tyr Ala Val Ala Ala Cys
 130 135 140

Ala Gly Thr Trp Leu Leu Leu Leu Thr Ala Leu Cys Pro Leu Ala Arg

145		150		155		160
Thr Asp Leu Thr Tyr Pro Val His Ala Leu Gly Ile Ile Thr Cys Phe						
	165		170		175	
Asp Val Leu Lys Trp Thr Met Leu Pro Ser Val Ala Met Trp Ala Val						
	180		185		190	
Phe Leu Phe Thr Ile Phe Ile Leu Leu Phe Leu Ile Pro Phe Val Ile						
	195		200		205	
Thr Val Ala Cys Tyr Thr Ala Thr Ile Leu Lys Leu Leu Arg Thr Glu						
	210		215		220	
Glu Ala His Gly Arg Glu Gln Arg Arg Arg Ala Val Gly Leu Ala Ala						
	225		230		235	240
Val Val Leu Leu Ala Phe Val Thr Cys Phe Ala Pro Asn Asn Phe Val						
		245		250		255
Leu Leu Ala His Ile Val Ser Arg Leu Phe Tyr Gly Lys Ser Tyr Tyr						
	260		265		270	
His Val Tyr Lys Leu Thr Leu Cys Leu Ser Cys Leu Asn Asn Cys Leu						
	275		280		285	
Asp Pro Phe Val Tyr Tyr Phe Ala Ser Arg Glu Phe Gln Leu Arg Leu						
	290		295		300	
Arg Glu Tyr Leu Gly Cys Arg Arg Val Pro Arg Asp Thr Leu Asp Thr						
	305		310		315	320
Arg Arg Glu Ser Leu Phe Ser Ala Arg Thr Thr Ser Val Arg Ser Glu						
		325		330		335
Ala Gly Ala His Pro Glu Gly Met Glu Gly Ala Thr Arg Pro Gly Leu						
	340		345		350	
Gln Arg Gln Glu Ser Val Phe						
	355					

<210> 29
 <211> 1503
 <212> DNA
 <213> Homo sapiens

 <400> 29


```

atggagcgtc cctgggagga cagcccaggc ccggaggggg cagctgaggg ctgcctgtg 60
ccagtcgccg ccggggcgcg ctccggtgcc gcggcgagtg gcacaggctg gcagccatgg 120
gctgagtgcc cgggacccaa ggggaggggg caactgctgg cgaccgccgg ccctttgcgt 180
cgctggcccc cccctcgcc tgccagctcc agccccgccc ccggagcggc gtccgctcac 240
tcggttcaag gcagcgcgac tgcgggtggc gcacgaccag ggcgcagacc ttggggcgcg 300
cggcccatgg agtcggggct gctgcggccg gcgccggtga gcgaggtcat cgtcctgcat 360
tacaactaca ccggcaagct ccgcggtgcg agctaccagc cgggtgccgg cctgcgcgcc 420
gacgccgtgg tgtgcctggc ggtgtgcgcc ttcatcgtgc tagagaatct agccgtgttg 480
ttggtgctcg gacgccaccc gcgcttcac gctcccatgt tcctgctcct gggcagcctc 540
acgttgctcg atctgctggc aggcgcgcc tacgcgccca acatcctact gtcggggccg 600
ctcacgctga aactgtcccc cgcgctctgg ttgcacggg agggagggcgt cttcgtggca 660
ctcactgctg ccgtgctgag cctcctggcc atcgcgctgg agcgcagcct caccatggcg 720
cgcagggggc ccgcgcccg ctccagtcgg ggcgcacgc tggcgatggc agccgcggcc 780
tggggcggtg cgctgctcct cgggctcctg ccagcgctgg gctggaattg cctgggtcgc 840
ctggacgctt gctccactgt cttgccgctc tacgccaagg cctacgtgct cttctgcgtg 900
ctgccttcg tgggcatcct ggccgcgatc tgtgcactct acgcgcgcat ctactgccag 960
gtacgcgcca acgcgcggcg cctgccggca cggcccggga ctgcggggac cacctcgacc 1020
cgggcgcgtc gcaagccgcg ctctctggcc ttgctgcgca cgctcagcgt ggtgctcctg 1080
gcctttgtgg catgttgggg cccctctctc ctgctgctgt tgctcgacgt ggcgtgcccg 1140
gcgcgcacct gtctgtact cctgcaggcc gatcccttc tgggactggc catggccaac 1200
tcacttctga accccatcat ctacacgctc accaaccgcg acctgcgcca cgcgctcctg 1260
cgcctggtct gctgcggacg ccaactcctgc ggcagagacc cgagtggctc ccagcagtcg 1320
gcgagcgcgg ctgaggcttc cgggggcctg cgccgctgcc tgccccggg ccttgatggg 1380
agcttcagcg gctcggagcg ctcatcgccc cagcgcgacg ggctggacac cagcggctcc 1440
acaggcagcc ccggtgcacc cacagccgcc cggactctgg tatcagaacc ggctgcagac 1500
tga 1503

```

<210> 30

<211> 500

<212> PRT

<213> Homo sapiens

<400> 30

```

Met Glu Arg Pro Trp Glu Asp Ser Pro Gly Pro Glu Gly Ala Ala Glu
  1             5             10            15

```

```

Gly Ser Pro Val Pro Val Ala Ala Gly Ala Arg Ser Gly Ala Ala Ala
      20            25            30

```

```

Ser Gly Thr Gly Trp Gln Pro Trp Ala Glu Cys Pro Gly Pro Lys Gly
      35            40            45

```

```

Arg Gly Gln Leu Leu Ala Thr Ala Gly Pro Leu Arg Arg Trp Pro Ala
      50            55            60

```

```

Pro Ser Pro Ala Ser Ser Ser Pro Ala Pro Gly Ala Ala Ser Ala His
      65            70            75            80

```

Ser Val Gln Gly Ser Ala Thr Ala Gly Gly Ala Arg Pro Gly Arg Arg
 85 90 95
 Pro Trp Gly Ala Arg Pro Met Glu Ser Gly Leu Leu Arg Pro Ala Pro
 100 105 110
 Val Ser Glu Val Ile Val Leu His Tyr Asn Tyr Thr Gly Lys Leu Arg
 115 120 125
 Gly Ala Ser Tyr Gln Pro Gly Ala Gly Leu Arg Ala Asp Ala Val Val
 130 135 140
 Cys Leu Ala Val Cys Ala Phe Ile Val Leu Glu Asn Leu Ala Val Leu
 145 150 155 160
 Leu Val Leu Gly Arg His Pro Arg Phe His Ala Pro Met Phe Leu Leu
 165 170 175
 Leu Gly Ser Leu Thr Leu Ser Asp Leu Leu Ala Gly Ala Ala Tyr Ala
 180 185 190
 Ala Asn Ile Leu Leu Ser Gly Pro Leu Thr Leu Lys Leu Ser Pro Ala
 195 200 205
 Leu Trp Phe Ala Arg Glu Gly Gly Val Phe Val Ala Leu Thr Ala Ser
 210 215 220
 Val Leu Ser Leu Leu Ala Ile Ala Leu Glu Arg Ser Leu Thr Met Ala
 225 230 235 240
 Arg Arg Gly Pro Ala Pro Val Ser Ser Arg Gly Arg Thr Leu Ala Met
 245 250 255
 Ala Ala Ala Ala Trp Gly Val Ser Leu Leu Leu Gly Leu Leu Pro Ala
 260 265 270
 Leu Gly Trp Asn Cys Leu Gly Arg Leu Asp Ala Cys Ser Thr Val Leu
 275 280 285
 Pro Leu Tyr Ala Lys Ala Tyr Val Leu Phe Cys Val Leu Ala Phe Val
 290 295 300
 Gly Ile Leu Ala Ala Ile Cys Ala Leu Tyr Ala Arg Ile Tyr Cys Gln
 305 310 315 320
 Val Arg Ala Asn Ala Arg Arg Leu Pro Ala Arg Pro Gly Thr Ala Gly
 325 330 335

Thr Thr Ser Thr Arg Ala Arg Arg Lys Pro Arg Ser Leu Ala Leu Leu
 340 345 350
 Arg Thr Leu Ser Val Val Leu Leu Ala Phe Val Ala Cys Trp Gly Pro
 355 360 365
 Leu Phe Leu Leu Leu Leu Leu Asp Val Ala Cys Pro Ala Arg Thr Cys
 370 375 380
 Pro Val Leu Leu Gln Ala Asp Pro Phe Leu Gly Leu Ala Met Ala Asn
 385 390 395 400
 Ser Leu Leu Asn Pro Ile Ile Tyr Thr Leu Thr Asn Arg Asp Leu Arg
 405 410 415
 His Ala Leu Leu Arg Leu Val Cys Cys Gly Arg His Ser Cys Gly Arg
 420 425 430
 Asp Pro Ser Gly Ser Gln Gln Ser Ala Ser Ala Ala Glu Ala Ser Gly
 435 440 445
 Gly Leu Arg Arg Cys Leu Pro Pro Gly Leu Asp Gly Ser Phe Ser Gly
 450 455 460
 Ser Glu Arg Ser Ser Pro Gln Arg Asp Gly Leu Asp Thr Ser Gly Ser
 465 470 475 480
 Thr Gly Ser Pro Gly Ala Pro Thr Ala Ala Arg Thr Leu Val Ser Glu
 485 490 495
 Pro Ala Ala Asp
 500

<210> 31
 <211> 1029
 <212> DNA
 <213> Homo sapiens

<400> 31
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 atcacaaatg gcctggcgat gaggattttc tttcaaatcc ggagtaaate aaactttatt 180
 atttttctta agaacacagt cattttctgat cttctcatga ttctgacttt tccattcaaa 240
 attcttagtg atgccaaact gggaacagga ccactgagaa cttttgtgtg tcaagttacc 300
 tccgtcatat tttattttcac aatgtatatc agtatttcat tcctgggact gataactatc 360
 gatcgctacc agaagaccac caggccattt aaaacatcca accccaaaaa tctcttgggg 420

gctaagattc tctctgttgt catctgggca ttcattgttct tactctcttt gcctaacatg 480
attctgacca acaggcagcc gagagacaag aatgtgaaga aatgctcttt ccttaaataca 540
gagttcggtc tagtctggca tgaaatagta aattacatct gtcaagtcatt tttctggatt 600
aatttcttaa ttgttattgt atgttatata ctcatataca aagaactgta ccggtcatac 660
gtaagaacga ggggtgtagg taaagtcccc aggaaaaagg tgaacgtcaa agttttcatt 720
atcattgctg tattctttat ttgttttgtt cctttccatt ttgccgaat tccttacacc 780
ctgagccaaa cccgggatgt ctttgactgc actgctgaaa atactctgtt ctatgtgaaa 840
gagagcactc tgtggttaac ttccttaaata gcatgcctgg atccgttcat ctattttttc 900
ctttgcaagt ccttcagaaa ttccttgata agtatgctga agtgcccaaa ttctgcaaca 960
tctctgtccc aggacaatag gaaaaaagaa caggatggtg gtgacccaaa tgaagagact 1020
ccaatgtaa 1029

<210> 32
<211> 342
<212> PRT
<213> Homo sapiens

<400> 32
Met Gln Ala Val Asp Asn Leu Thr Ser Ala Pro Gly Asn Thr Ser Leu
1 5 10 15
Cys Thr Arg Asp Tyr Lys Ile Thr Gln Val Leu Phe Pro Leu Leu Tyr
20 25 30
Thr Val Leu Phe Phe Val Gly Leu Ile Thr Asn Gly Leu Ala Met Arg
35 40 45
Ile Phe Phe Gln Ile Arg Ser Lys Ser Asn Phe Ile Ile Phe Leu Lys
50 55 60
Asn Thr Val Ile Ser Asp Leu Leu Met Ile Leu Thr Phe Pro Phe Lys
65 70 75 80
Ile Leu Ser Asp Ala Lys Leu Gly Thr Gly Pro Leu Arg Thr Phe Val
85 90 95
Cys Gln Val Thr Ser Val Ile Phe Tyr Phe Thr Met Tyr Ile Ser Ile
100 105 110
Ser Phe Leu Gly Leu Ile Thr Ile Asp Arg Tyr Gln Lys Thr Thr Arg
115 120 125
Pro Phe Lys Thr Ser Asn Pro Lys Asn Leu Leu Gly Ala Lys Ile Leu
130 135 140
Ser Val Val Ile Trp Ala Phe Met Phe Leu Leu Ser Leu Pro Asn Met
145 150 155 160

Ile	Leu	Thr	Asn	Arg	Gln	Pro	Arg	Asp	Lys	Asn	Val	Lys	Lys	Cys	Ser	165	170	175	
Phe	Leu	Lys	Ser	Glu	Phe	Gly	Leu	Val	Trp	His	Glu	Ile	Val	Asn	Tyr	180	185	190	
Ile	Cys	Gln	Val	Ile	Phe	Trp	Ile	Asn	Phe	Leu	Ile	Val	Ile	Val	Cys	195	200	205	
Tyr	Thr	Leu	Ile	Thr	Lys	Glu	Leu	Tyr	Arg	Ser	Tyr	Val	Arg	Thr	Arg	210	215	220	
Gly	Val	Gly	Lys	Val	Pro	Arg	Lys	Lys	Val	Asn	Val	Lys	Val	Phe	Ile	225	230	235	240
Ile	Ile	Ala	Val	Phe	Phe	Ile	Cys	Phe	Val	Pro	Phe	His	Phe	Ala	Arg	245	250	255	
Ile	Pro	Tyr	Thr	Leu	Ser	Gln	Thr	Arg	Asp	Val	Phe	Asp	Cys	Thr	Ala	260	265	270	
Glu	Asn	Thr	Leu	Phe	Tyr	Val	Lys	Glu	Ser	Thr	Leu	Trp	Leu	Thr	Ser	275	280	285	
Leu	Asn	Ala	Cys	Leu	Asp	Pro	Phe	Ile	Tyr	Phe	Phe	Leu	Cys	Lys	Ser	290	295	300	
Phe	Arg	Asn	Ser	Leu	Ile	Ser	Met	Leu	Lys	Cys	Pro	Asn	Ser	Ala	Thr	305	310	315	320
Ser	Leu	Ser	Gln	Asp	Asn	Arg	Lys	Lys	Glu	Gln	Asp	Gly	Gly	Asp	Pro	325	330	335	
Asn	Glu	Glu	Thr	Pro	Met											340			

<210> 33
 <211> 1077
 <212> DNA
 <213> Homo sapiens

<400> 33
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 gccacaggca cagccttcct gctgctggcg gcgctgctgg ggctgcctgg caacggcttc 120
 gtggtgtgga gcttggcggg ctggcggcct gcacgggggc gaccgctggc ggccacgctt 180
 gtgctgcacc tggcgctggc cgacggcgcg gtgctgctgc tcacgccgct ctttgtggcc 240

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ttcctgaccc ggcaggcctg gccgctgggc caggcgggct gcaaggcggg gtactacgtg 300
tgcgcgctca gcatgtacgc cagcgtgctg ctcaccggcc tgctcagcct gcagcgtgc 360
ctcgcagtc cccgccccctt cctgggcgct cggtgcgca gcccggccct ggcccgcgc 420
ctgctgctgg cggctctggct ggccgccttg ttgctcgccg tcccggccgc cgtctaccgc 480
cacctgtgga gggaccgcgt atgccagctg tgccaccgct cgccggtcca cgccgcgcgc 540
cacctgagcc tggagactct gaccgctttc gtgcttcctt tcgggctgat gtcgggctgc 600
tacagcgtga cgctggcacg gctgcggggc gcccgctggg gctccggggc gcacggggcg 660
cgggtgggcc ggctgggtgag cgccatcgtg cttgccttcg gcttgctctg ggccccctac 720
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aagctggggc gagccggcca ggcggcgcga gcgggaacta cggccttggc cttcttcagt 840
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ccccgtttcc tcacgcggct cttcgaaggc tctggggagg cccgaggggg cgccgcgtct 960
agggaaggga ccatggagct ccgaactacc cctcagctga aagtgggtgg gcaggggcgc 1020
ggcaatggag acccgggggg tgggatggag aaggacggct cggaatggga cctttga 1077

```

<210> 34
 <211> 358
 <212> PRT
 <213> Homo sapiens

<400> 34

```

Met Ser Val Cys Tyr Arg Pro Pro Gly Asn Glu Thr Leu Leu Ser Trp
  1              5              10              15

```

```

Lys Thr Ser Arg Ala Thr Gly Thr Ala Phe Leu Leu Leu Ala Ala Leu
      20              25              30

```

```

Leu Gly Leu Pro Gly Asn Gly Phe Val Val Trp Ser Leu Ala Gly Trp
    35              40              45

```

```

Arg Pro Ala Arg Gly Arg Pro Leu Ala Ala Thr Leu Val Leu His Leu
    50              55              60

```

```

Ala Leu Ala Asp Gly Ala Val Leu Leu Leu Thr Pro Leu Phe Val Ala
    65              70              75              80

```

```

Phe Leu Thr Arg Gln Ala Trp Pro Leu Gly Gln Ala Gly Cys Lys Ala
      85              90              95

```

```

Val Tyr Tyr Val Cys Ala Leu Ser Met Tyr Ala Ser Val Leu Leu Thr
    100              105              110

```

```

Gly Leu Leu Ser Leu Gln Arg Cys Leu Ala Val Thr Arg Pro Phe Leu
    115              120              125

```

```

Ala Pro Arg Leu Arg Ser Pro Ala Leu Ala Arg Arg Leu Leu Leu Ala
    130              135              140

```

Val Trp Leu Ala Ala Leu Leu Leu Ala Val Pro Ala Ala Val Tyr Arg
 145 150 155 160
 His Leu Trp Arg Asp Arg Val Cys Gln Leu Cys His Pro Ser Pro Val
 165 170 175
 His Ala Ala Ala His Leu Ser Leu Glu Thr Leu Thr Ala Phe Val Leu
 180 185 190
 Pro Phe Gly Leu Met Leu Gly Cys Tyr Ser Val Thr Leu Ala Arg Leu
 195 200 205
 Arg Gly Ala Arg Trp Gly Ser Gly Arg His Gly Ala Arg Val Gly Arg
 210 215 220
 Leu Val Ser Ala Ile Val Leu Ala Phe Gly Leu Leu Trp Ala Pro Tyr
 225 230 235 240
 His Ala Val Asn Leu Leu Gln Ala Val Ala Ala Leu Ala Pro Pro Glu
 245 250 255
 Gly Ala Leu Ala Lys Leu Gly Gly Ala Gly Gln Ala Ala Arg Ala Gly
 260 265 270
 Thr Thr Ala Leu Ala Phe Phe Ser Ser Ser Val Asn Pro Val Leu Tyr
 275 280 285
 Val Phe Thr Ala Gly Asp Leu Leu Pro Arg Ala Gly Pro Arg Phe Leu
 290 295 300
 Thr Arg Leu Phe Glu Gly Ser Gly Glu Ala Arg Gly Gly Gly Arg Ser
 305 310 315 320
 Arg Glu Gly Thr Met Glu Leu Arg Thr Thr Pro Gln Leu Lys Val Val
 325 330 335
 Gly Gln Gly Arg Gly Asn Gly Asp Pro Gly Gly Gly Met Glu Lys Asp
 340 345 350
 Gly Pro Glu Trp Asp Leu
 355

<210> 35
 <211> 1005
 <212> DNA
 <213> Homo sapiens

<400> 35

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aataccattg ttgtttacgg ctacatcttc tctctgaaga actggaacag cagtaatatt 180
tatctcttta acctctctgt ctctgaacta gcttttctgt gcaccctccc catgctgata 240
aggagttatg ccaatggaaa ctggatatat ggagacgtgc tctgcataag caaccgatat 300
gtgcttcatg ccaacctcta taccagcatt ctctttctca cttttatcag catagatcga 360
tacttgataa ttaagtatcc tttccgagaa caccttctgc aaaagaaaga gtttgctatt 420
ttaatctcct tggccatttg ggtttttagta accttagagt tactacctat acttcccctt 480
ataaatcctg ttataactga caatggcacc acctgtaatg attttgcaag ttctggagac 540
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tttgtgatgt gtttctttta ttacaagatt gctctcttcc taaagcagag gaataggcag 660
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<211> 334

<212> PRT

<213> Homo sapiens

<400> 36

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Ala Glu Ala Ala Leu Glu Lys Tyr Tyr Leu Ser Ile Phe Tyr Gly Ile
      20             25             30

Glu Phe Val Val Gly Val Leu Gly Asn Thr Ile Val Val Tyr Gly Tyr
      35             40             45

Ile Phe Ser Leu Lys Asn Trp Asn Ser Ser Asn Ile Tyr Leu Phe Asn
      50             55             60

Leu Ser Val Ser Asp Leu Ala Phe Leu Cys Thr Leu Pro Met Leu Ile
      65             70             75             80

Arg Ser Tyr Ala Asn Gly Asn Trp Ile Tyr Gly Asp Val Leu Cys Ile
      85             90             95

Ser Asn Arg Tyr Val Leu His Ala Asn Leu Tyr Thr Ser Ile Leu Phe
      100            105            110
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Leu Thr Phe Ile Ser Ile Asp Arg Tyr Leu Ile Ile Lys Tyr Pro Phe
 115 120 125
 Arg Glu His Leu Leu Gln Lys Lys Glu Phe Ala Ile Leu Ile Ser Leu
 130 135 140
 Ala Ile Trp Val Leu Val Thr Leu Glu Leu Leu Pro Ile Leu Pro Leu
 145 150 155 160
 Ile Asn Pro Val Ile Thr Asp Asn Gly Thr Thr Cys Asn Asp Phe Ala
 165 170 175
 Ser Ser Gly Asp Pro Asn Tyr Asn Leu Ile Tyr Ser Met Cys Leu Thr
 180 185 190
 Leu Leu Gly Phe Leu Ile Pro Leu Phe Val Met Cys Phe Phe Tyr Tyr
 195 200 205
 Lys Ile Ala Leu Phe Leu Lys Gln Arg Asn Arg Gln Val Ala Thr Ala
 210 215 220
 Leu Pro Leu Glu Lys Pro Leu Asn Leu Val Ile Met Ala Val Val Ile
 225 230 235 240
 Phe Ser Val Leu Phe Thr Pro Tyr His Val Met Arg Asn Val Arg Ile
 245 250 255
 Ala Ser Arg Leu Gly Ser Trp Lys Gln Tyr Gln Cys Thr Gln Val Val
 260 265 270
 Ile Asn Ser Phe Tyr Ile Val Thr Arg Pro Leu Ala Phe Leu Asn Ser
 275 280 285
 Val Ile Asn Pro Val Phe Tyr Phe Leu Leu Gly Asp His Phe Arg Asp
 290 295 300
 Met Leu Met Asn Gln Leu Arg His Asn Phe Lys Ser Leu Thr Ser Phe
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 Ser Arg Trp Ala His Glu Leu Leu Leu Ser Phe Arg Glu Lys
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<211> 1296

<212> DNA

<213> Homo sapiens

<400> 37

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gtggaaaggc accagggact tgtgcatcct tttaaaatga agtggcaata caccaaccga 480
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<210> 38

<211> 431

<212> PRT

<213> Homo sapiens

<400> 38

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  1             5             10             15

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Asp His Asn Leu Thr Arg Glu Gln Phe Ile Ala Leu Tyr Arg Leu Arg
      20             25             30

```

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Pro Leu Val Tyr Thr Pro Glu Leu Pro Gly Arg Ala Lys Leu Ala Leu
    35             40             45

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Val Leu Thr Gly Val Leu Ile Phe Ala Leu Ala Leu Phe Gly Asn Ala
    50             55             60

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Leu Val Phe Tyr Val Val Thr Arg Ser Lys Ala Met Arg Thr Val Thr
    65             70             75             80

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Asn Ile Phe Ile Cys Ser Leu Ala Leu Ser Asp Leu Leu Ile Thr Phe
      85             90             95

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Phe	Cys	Ile	Pro	Val	Thr	Met	Leu	Gln	Asn	Ile	Ser	Asp	Asn	Trp	Leu	100	105	110
Gly	Gly	Ala	Phe	Ile	Cys	Lys	Met	Val	Pro	Phe	Val	Gln	Ser	Thr	Ala	115	120	125
Val	Val	Thr	Glu	Met	Leu	Thr	Met	Thr	Cys	Ile	Ala	Val	Glu	Arg	His	130	135	140
Gln	Gly	Leu	Val	His	Pro	Phe	Lys	Met	Lys	Trp	Gln	Tyr	Thr	Asn	Arg	145	150	155
Arg	Ala	Phe	Thr	Met	Leu	Gly	Val	Val	Trp	Leu	Val	Ala	Val	Ile	Val	165	170	175
Gly	Ser	Pro	Met	Trp	His	Val	Gln	Gln	Leu	Glu	Ile	Lys	Tyr	Asp	Phe	180	185	190
Leu	Tyr	Glu	Lys	Glu	His	Ile	Cys	Cys	Leu	Glu	Glu	Trp	Thr	Ser	Pro	195	200	205
Val	His	Gln	Lys	Ile	Tyr	Thr	Thr	Phe	Ile	Leu	Val	Ile	Leu	Phe	Leu	210	215	220
Leu	Pro	Leu	Met	Val	Met	Leu	Ile	Leu	Tyr	Ser	Lys	Ile	Gly	Tyr	Glu	225	230	235
Leu	Trp	Ile	Lys	Lys	Arg	Val	Gly	Asp	Gly	Ser	Val	Leu	Arg	Thr	Ile	245	250	255
His	Gly	Lys	Glu	Met	Ser	Lys	Ile	Ala	Arg	Lys	Lys	Lys	Arg	Ala	Val	260	265	270
Ile	Met	Met	Val	Thr	Val	Val	Ala	Leu	Phe	Ala	Val	Cys	Trp	Ala	Pro	275	280	285
Phe	His	Val	Val	His	Met	Met	Ile	Glu	Tyr	Ser	Asn	Phe	Glu	Lys	Glu	290	295	300
Tyr	Asp	Asp	Val	Thr	Ile	Lys	Met	Ile	Phe	Ala	Ile	Val	Gln	Ile	Ile	305	310	315
Gly	Phe	Ser	Asn	Ser	Ile	Cys	Asn	Pro	Ile	Val	Tyr	Ala	Phe	Met	Asn	325	330	335
Glu	Asn	Phe	Lys	Lys	Asn	Val	Leu	Ser	Ala	Val	Cys	Tyr	Cys	Ile	Val	340	345	350

Asn Lys Thr Phe Ser Pro Ala Gln Arg His Gly Asn Ser Gly Ile Thr
 355 360 365

Met Met Arg Lys Lys Ala Lys Phe Ser Leu Arg Glu Asn Pro Val Glu
 370 375 380

Glu Thr Lys Gly Glu Ala Phe Ser Asp Gly Asn Ile Glu Val Lys Leu
 385 390 395 400

Cys Glu Gln Thr Glu Glu Lys Lys Lys Leu Lys Arg His Leu Ala Leu
 405 410 415

Phe Arg Ser Glu Leu Ala Glu Asn Ser Pro Leu Asp Ser Gly His
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31

<210> 42
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<400> 42
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32

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<400> 44
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<210> 45
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<400> 45
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aagagtggac cagccctgtg caccagaaga tctacaccac cttcatcctt gtcacacctt 180
tcctcctgcc tcttatgggtg atgcttattc tgtacgtaaa attgggttatg aactttggat 240
aaagaaaaga gttgggggatg gttcagtgct tcgaactatt catggaaaag aaatgtccaa 300
aatagccagg aagaagaaac gagctgtcat tatgatgggtg acagtgggtgg ctctctttgc 360
tgtgtgctgg gcaccattcc atgttgtcca tatgatgatt gaatacagta attttgaaaa 420
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<400> 58
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<210> 69
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<400> 69
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<400> 70
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<400> 71
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<210> 72
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<210> 73
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<400> 73
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<210> 74
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27